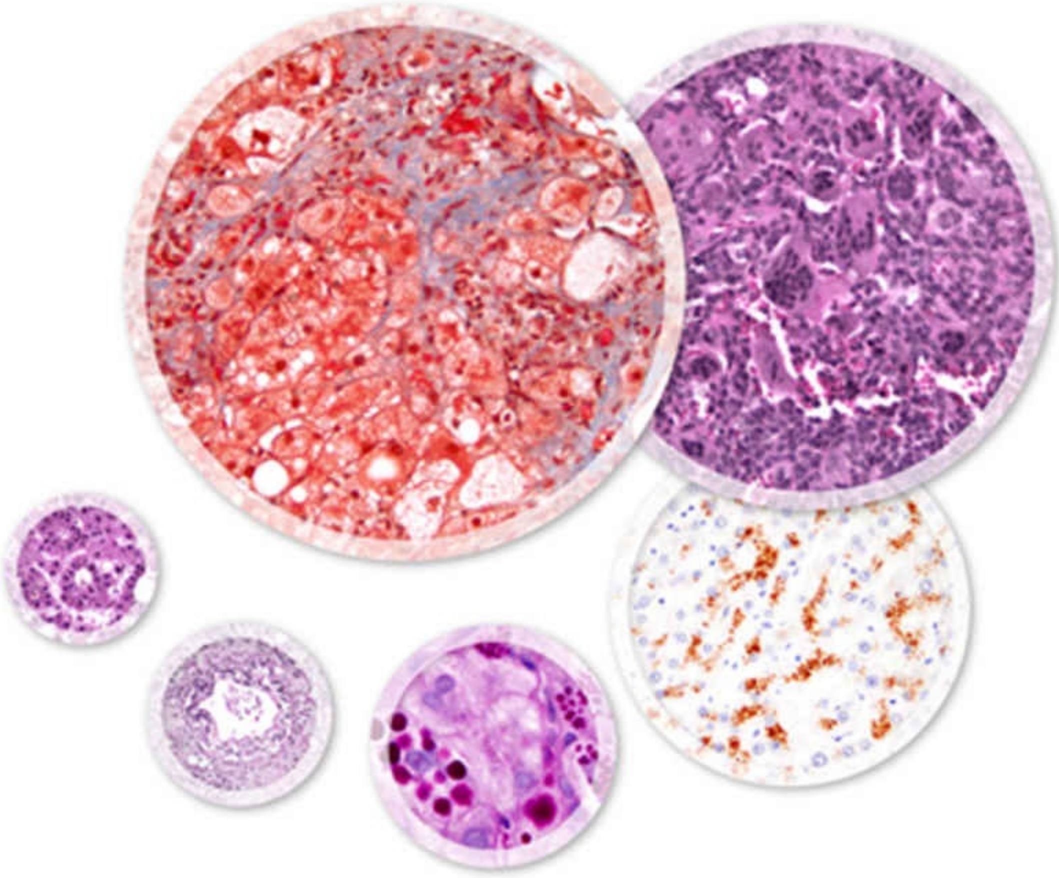
DIAGNOSTIC PATHOLOGY

Hepatobiliary and Pancreas

SECOND EDITION

LAMPS | KAKAR



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DIAGNOSTIC PATHOLOGY: Hepatobiliary and Pancreas

SECOND EDITION

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Dedications

For all hepatophiles—past, present, and future.

LL

Dedicated to the art and science of liver pathology, which I indulge in during working hours, as a tribute to patients whom I see only through a kaleidoscope of colors.

SK

To my husband, my family, and my colleagues, for all they have taught me about how to teach and how to learn.

LY

To my family and my colleagues, for their unreserved support.

HW

I'd like to dedicate my contribution in this book to my family.

MY

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Preface

Medical liver disease often poses a challenge for surgical pathologists, for a wide variety of disease processes produce a relatively limited number of histologic pictures. Tumors of the liver, pancreas, and biliary system may also present diagnostic challenges, especially if infrequently encountered. *Diagnostic Pathology: Hepatobiliary and Pancreas*, second edition is designed to help both practicing pathologists and pathologists in training address these dilemmas when they arise.

This reference provides clear, concise, up-to-date information on hepatobiliary and pancreatic pathology, along with a wealth of images (if a picture is worth a thousand words, then there are at least 1,100,000 words' worth of images in this book). The images include photomicrographs, gross photographs, and beautiful medical illustrations, many of which were created especially for this book. As with all of the books in the *Diagnostic Pathology* series, the key facts pertaining to each diagnosis are highlighted in a box for ease of use. A list of important entities in the differential diagnosis section is given for each diagnosis, with electronic links to every DDx in the electronic product, Expert Consult.

On behalf of all of the authors of this book, we hope that *Diagnostic Pathology: Hepatobiliary and Pancreas*, second edition will prove to be a favorite reference to which pathologists turn again and again in their daily practice.

Laura W. Lamps, MD, *Professor and Vice Chair for Academic Affairs, Department of Pathology, University of Arkansas for Medical Sciences, Little Rock, Arkansas*

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Sections

PART I
Liver

OUTLINE

SECTION 1
INHERITED, METABOLIC, AND DEVELOPMENTAL DISORDERS

OUTLINE

Glycogen Storage Disease

KEY FACTS

Etiology/Pathogenesis

- Inborn error of carbohydrate metabolism caused by gene mutations in proteins involved in glycogen synthesis, degradation, or regulation
  - Results in different enzymatic defects in liver that are classified as glycogen storage disease (GSD) types 0, I, II, III, IV, VI, and IX
  - Types I, III, and IX account for 80% of hepatic GSD
- Most forms autosomal recessive, except GSD IX, which is X-linked

Clinical Issues

- Most patients present with hepatomegaly and hypoglycemia
- Increased incidence of hepatic adenoma and hepatocellular carcinoma in GSD I and also GSD III
- Liver transplantation corrects primary hepatic enzyme defect and is used primarily for GSD IV
- Prognosis variable based on type of GSD

Microscopic

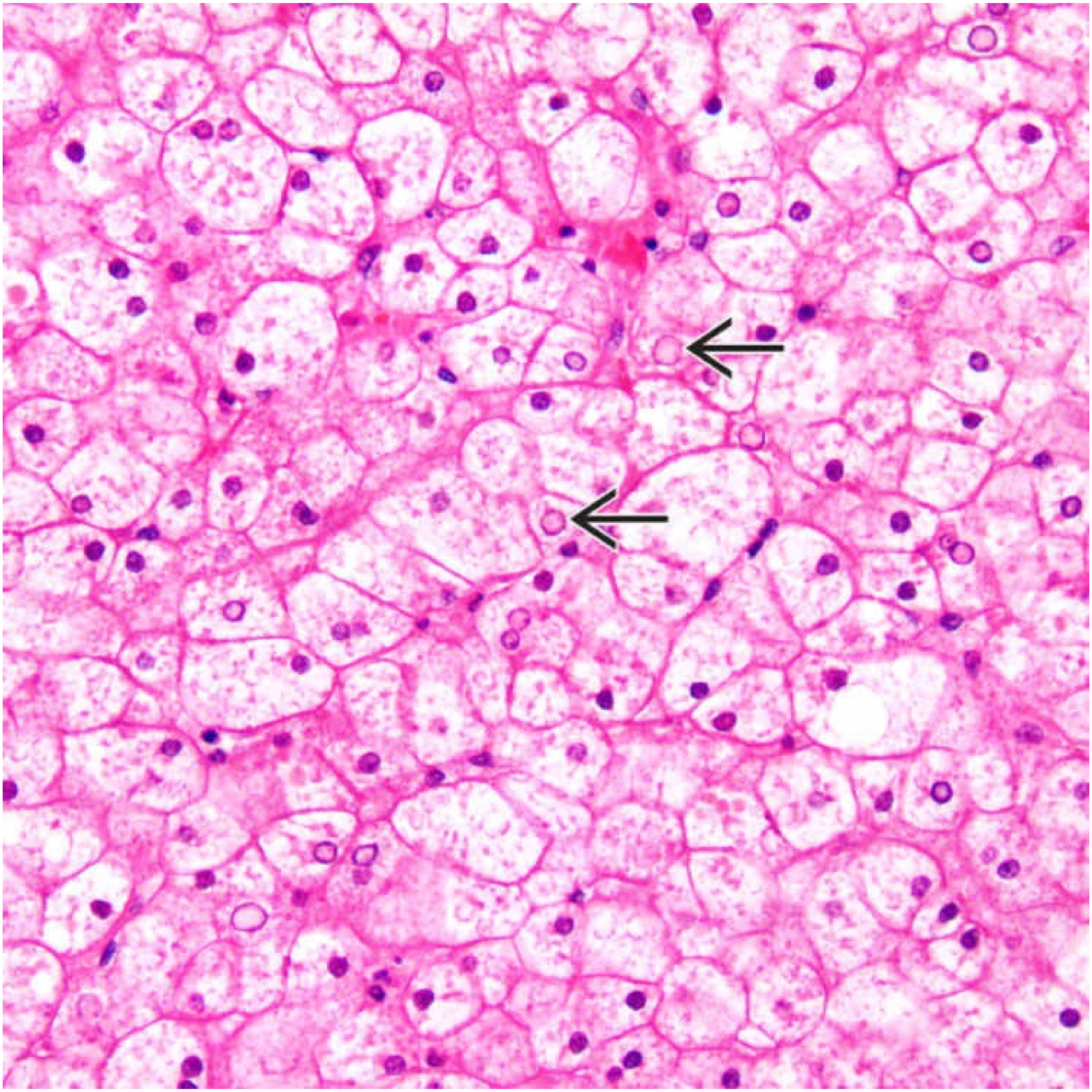
- Histologic features not generally diagnostic of GSD
  - Assess liver for mosaic pattern of hepatocytes, glycogenated nuclei, fatty change, and fibrosis
  - Enlarged, pale-staining, swollen hepatocyte cytoplasm, and prominent cell membrane appearance
  - Compression of sinusoids by expanded hepatocytes
  - GSD 0 has decreased glycogen
  - GSD IV has characteristic cytoplasmic inclusions
- Cirrhosis frequent in GSD IV and can occur in III and IX

Ancillary Tests

- Electron microscopy
  - Lysosomal-bound glycogen for GSD II
  - Fibrillar glycogen for GSD IV

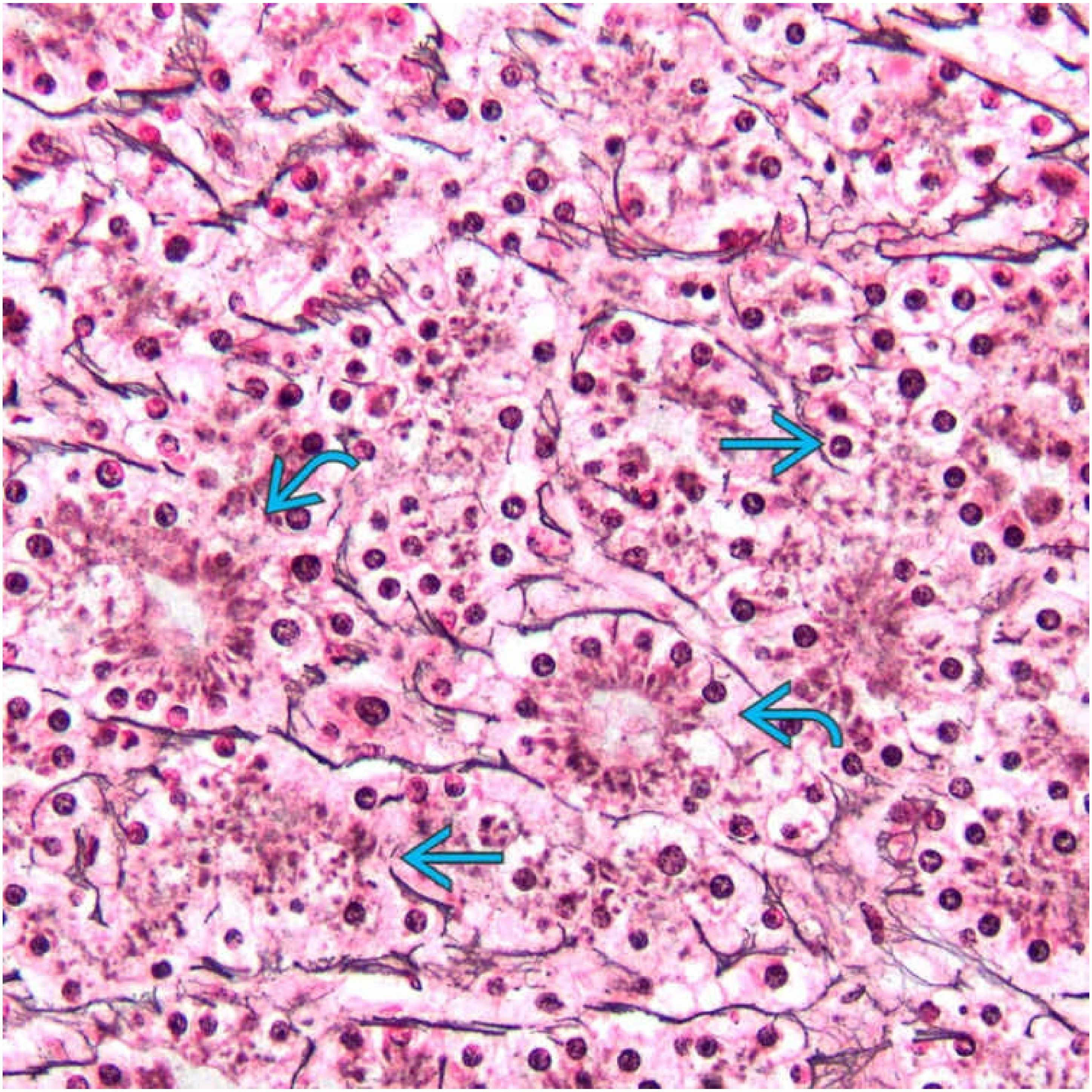
Top Differential Diagnoses

• Glycogenic hepatopathy



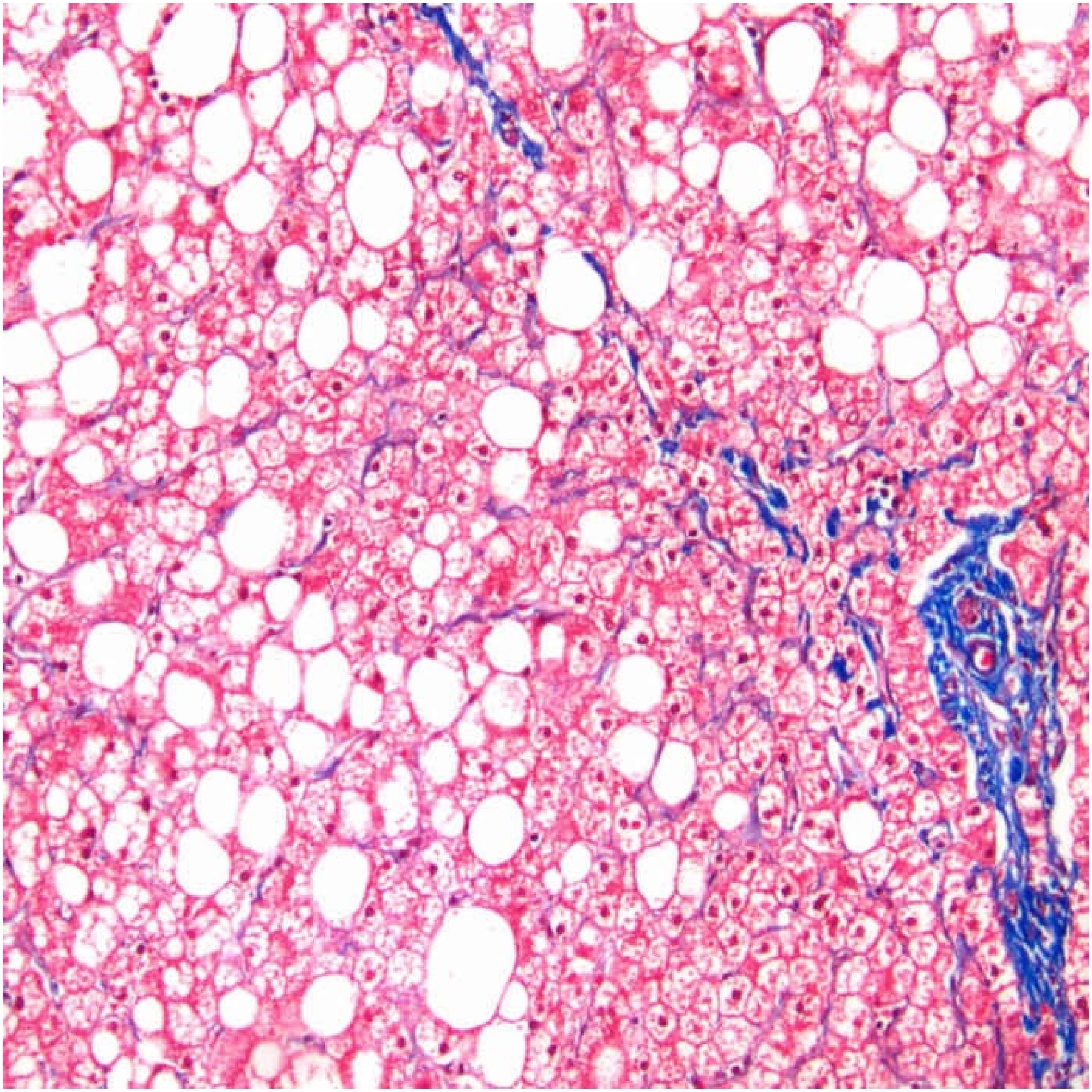
Mosaic Pattern in GSD Ia

The mosaic pattern results from swollen hepatocytes compressing the sinusoids. The cell membranes are accentuated, and prominent glycogenated nuclei → are seen.



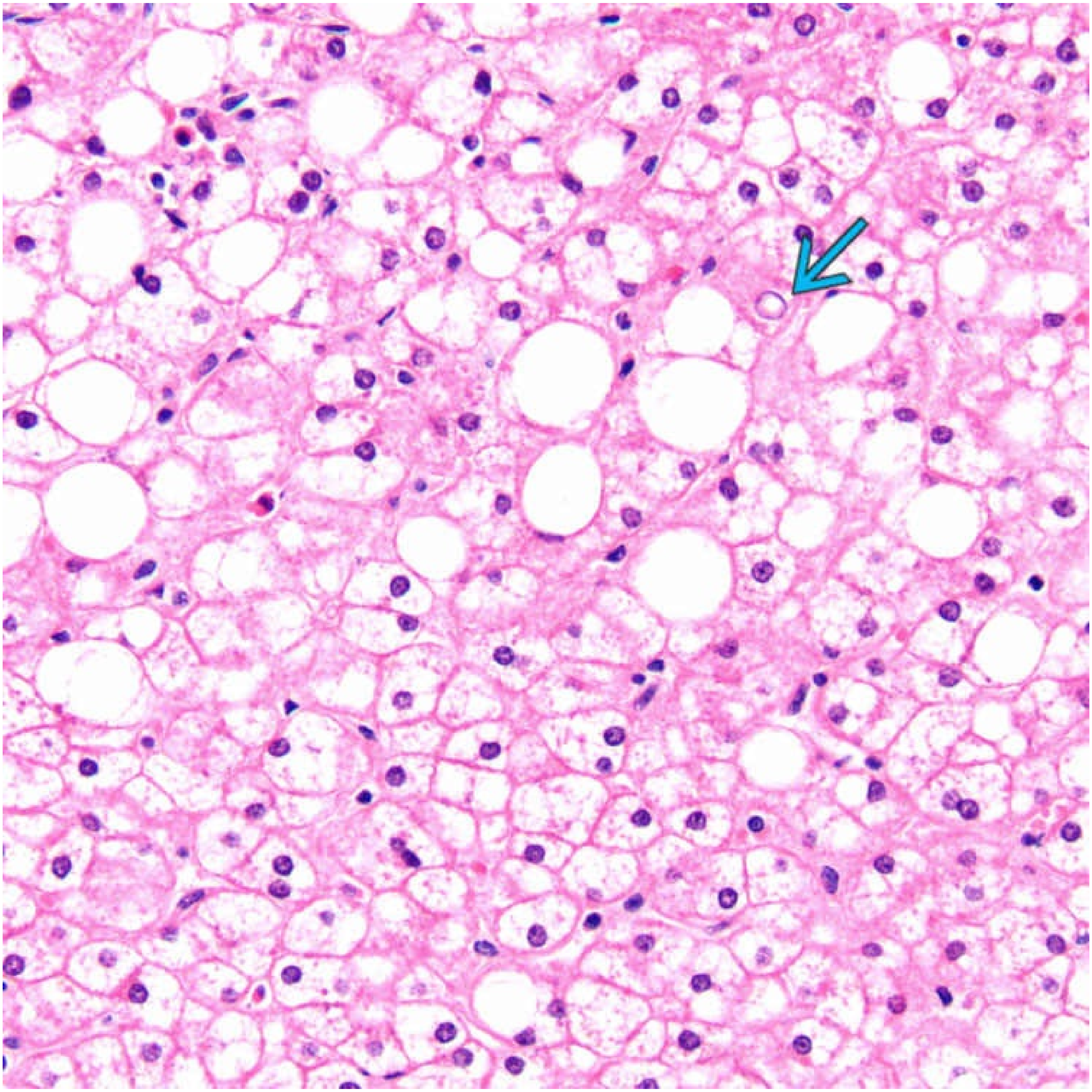
Hepatocellular Carcinoma in GSD Ia

Reticulin stain highlights the abnormal architecture, loss of reticulin fibers →, and pseudorosette formation ↱ in this hepatocellular carcinoma arising in a patient with glycogen storage disease (GSD) Ia.



Steatosis and Fibrosis in GSD Ia

Prominent large and small droplet fat as well as periportal fibrosis is depicted in this case of GSD Ia.



Enlarged Hepatocytes in GSD Ib
The findings in this case of GSD Ib are similar to those observed in GSD Ia. Pale, enlarged hepatocytes with inconspicuous sinusoids contain only a rare glycogenated nucleus →. Fatty change is more apparent in this focus.

TERMINOLOGY

Abbreviations

- Glycogen storage disease (GSD)

Synonyms

- Glycogenoses

ETIOLOGY/PATHOGENESIS

Inborn Error of Carbohydrate Metabolism

- Gene mutation causes deficiency of hepatic enzymes involved in glycogen synthesis, degradation, or regulation
  - GSD I, II, III, IV, VI, and IX display increased hepatic glycogen
  - GSD 0 is storage defect that results in decreased hepatic glycogen
- Types I, III, and IX account for 80% of hepatic GSD
- Most forms autosomal recessive, except GSD IX, which is X-linked

CLINICAL ISSUES

Presentation

- Hepatomegaly: GSD I, III, IV, VI, IX, and rarely in GSD II
  - GSD VI also causes short stature and hyperlipidemia
- Hypoglycemia
  - GSD Ia, Ib, III: Hypoglycemia in infancy due to inability to maintain steady blood glucose levels between feedings
    - Profound hypoglycemia can result in seizures
  - GSD 0: Hypoglycemia after short fasts, often in early childhood as feed intervals are extended
  - Hypoglycemia mild in GSD VI and IX, rare in GSD IV; not feature of GSD II

Laboratory Tests

- Enzymatic activity assay in liver tissue
  - GSD Ia, III, IV, VI, and IX
- DNA mutational analysis

Treatment

- Dietary intervention to prevent hypoglycemia, particularly for GSD 0 and I, also in GSD III
  - Liver transplantation corrects primary hepatic enzyme defect
  - Best treatment option for GSD IV; also has been performed for GSD I, III, and IV

Prognosis

- Variable based on type of GSD
  - Some patients well controlled
  - Can lead to life-threatening complications including liver, heart, and respiratory failure
- Increased incidence of hepatocellular neoplasia
  - Hepatic adenoma is frequent in GSD I, can occur in GSD III
  - Hepatocellular carcinoma occurs in GSD I; also reported in GSD III

MICROSCOPIC

Histologic Features

- Usually not diagnostic of GSD
  - Exception is characteristic cytoplasmic inclusion in GSD IV
  - – Weakly basophilic to colorless inclusion, retracts from surrounding cytoplasm
  - – PAS positive and partially digested on PAS-D
- Mosaic appearance: GSD I, III, VI, and IX
  - Enlarged, pale-staining hepatocyte cytoplasm, prominent cell membranes, and compression of sinusoids
  - Excess glycogen is PAS positive, PAS-D negative
    - – Glycogen may wash out with formalin processing, can be retained with alcohol fixation
- Fibrosis: GSD III, IV, VI, IX; may occur in GSD I
  - Frequently progresses to cirrhosis in GSD IV and also can occur in III and IX
- Hepatocyte features
  - Glycogenated nuclei: In GSD I (prominent) and III (less), but not specific for GSD
  - Thickened cytoplasmic membrane resulting from organelles at periphery of cytoplasm
- Cytoplasmic lipid in all GSD but more pronounced in GSD I

Ultrastructural Features

- GSD 0: Nonspecific with sparse glycogen
  - GSD I: Glycogen displaces organelles, large lipid droplets, and prominent intranuclear glycogen
  - GSD II: Lysosomal monoparticulate glycogen
  - GSD III: Similar to GSD I, but less lipid and nuclear glycogen
  - GSD IV: Fibrillar glycogen and glycogen rosettes
  - GSD VI: Cytoplasmic monoparticulate glycogen and glycogen rosettes displace organelles
  - Resembles starry-sky of GSD IX
- GSD IX: Starry-sky appearance of dense areas of cytoplasmic glycogen alternating with organelle-free zones
  - Displacement of organelles to cell margin
  - Glycogen is mixture of monoparticulated and multiparticulated forms
- Lipid may be present in all hepatic GSD on ultrastructural studies
- Intracellular collagen has been demonstrated in GSD III and IV

DIFFERENTIAL DIAGNOSIS

Glycogenic Hepatopathy

- Histologic overlap with GSD but distinct clinical picture of type 1 diabetes mellitus with poorly controlled blood glucose

Treated Urea Cycle Defects

- Can result in hepatocyte glycogen accumulation, possibly related to therapeutic dietary modification
  - Nonuniform distribution of glycogen and no displacement of organelles

Lafora Disease

- Lafora bodies are more eosinophilic and stain homogeneously with colloidal iron
- GSD IV can show nonspecific colloidal iron staining but with a clumpy granular pattern

Fibrinogen Storage Disease

- Eosinophilic spherical and vacuolated inclusions immunoreactive for fibrinogen
  - Ultrastructurally composed of finger-like pattern inclusion in rough endoplasmic reticulum

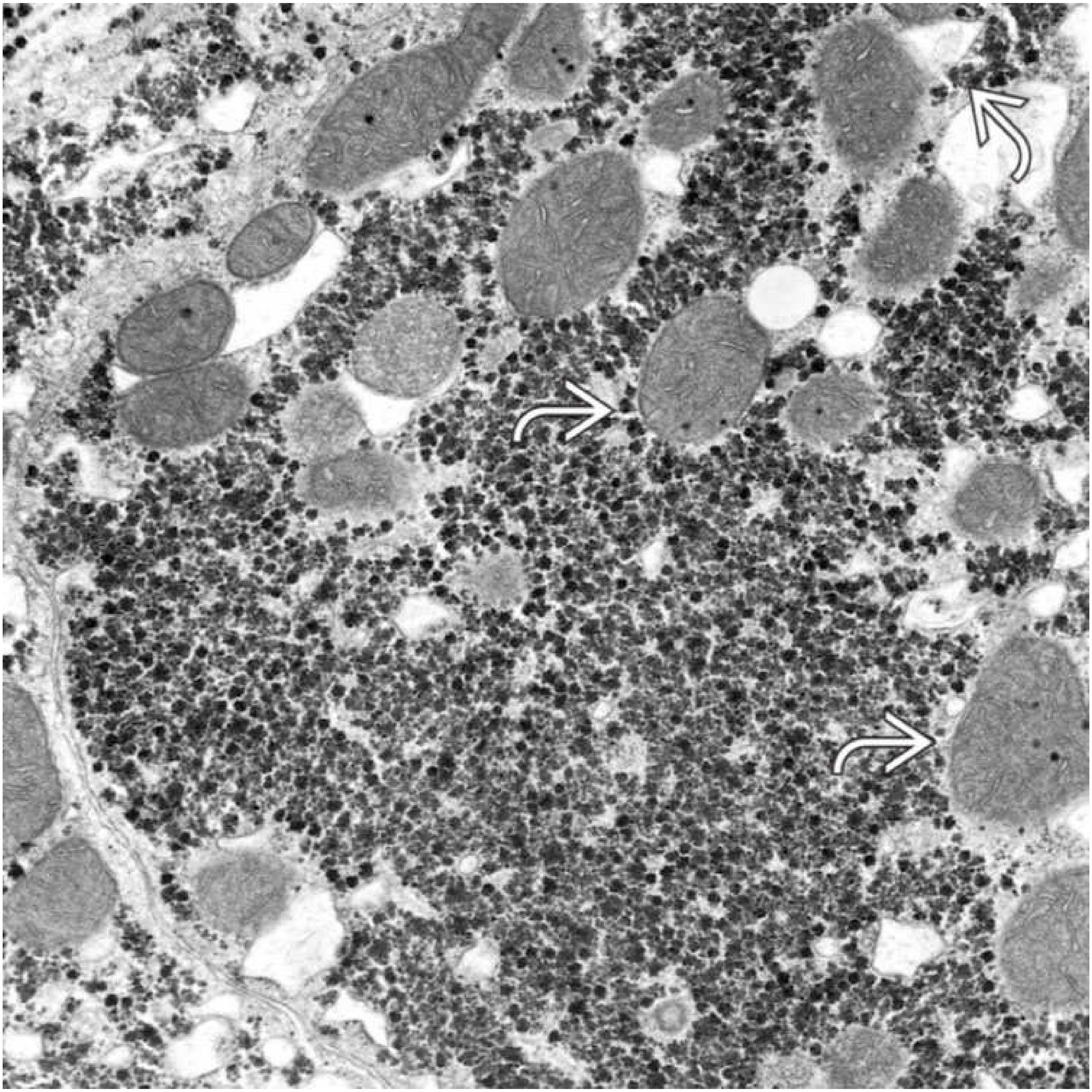
Other Entities With Prominent Inclusions

- Ground-glass inclusions of hepatitis B
- Drug-associated morphologic change (e.g., cyanamide)

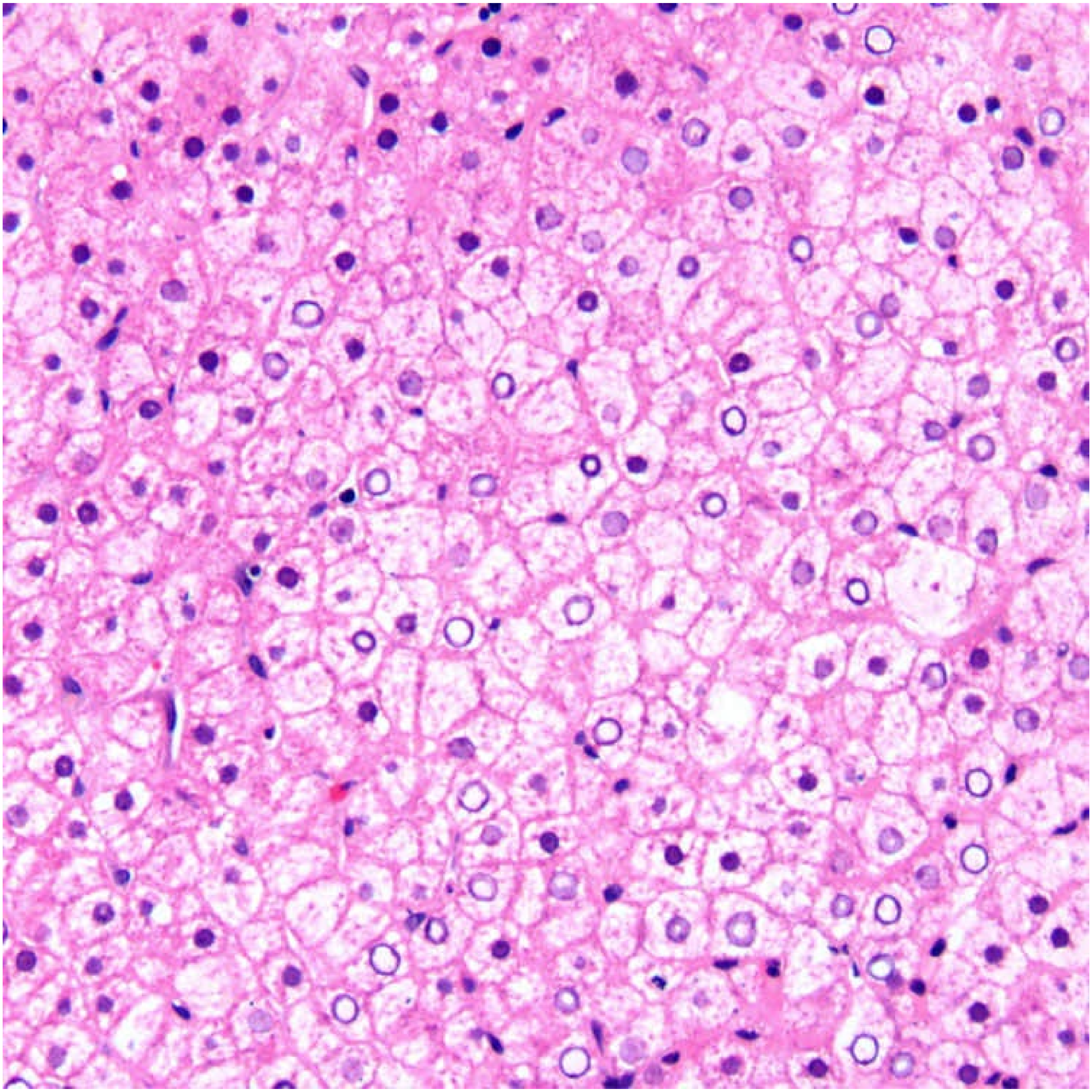
DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

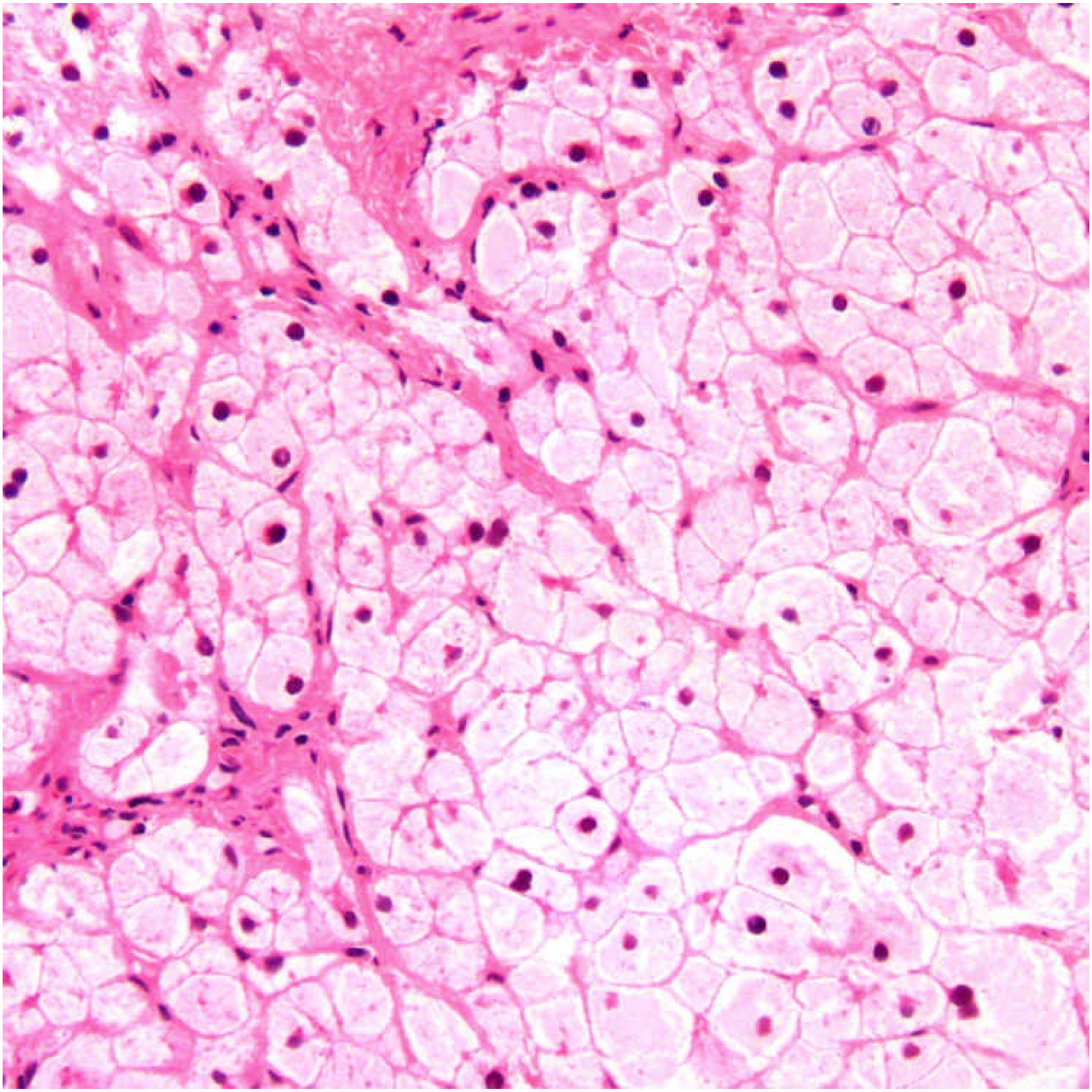
- Increased hepatic glycogen in all hepatic GSD except GSD 0
  - Diagnostic ultrastructural feature for GSD II
  - Lysosomal-bound glycogen
- Unique cytoplasmic inclusion in GSD IV
  - Pathognomic cytoplasmic inclusions composed of fibrillar glycogen by electron microscopy



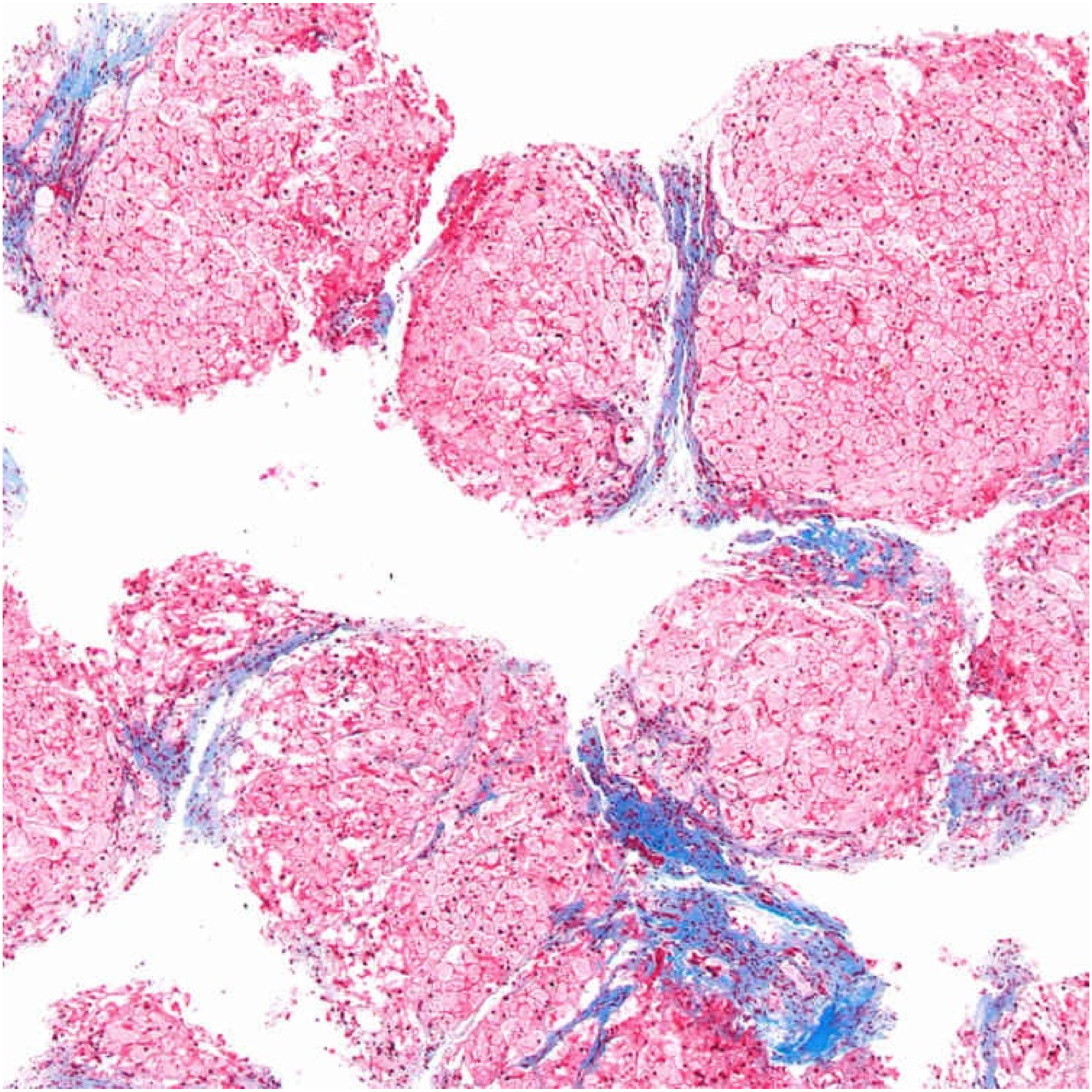
Glycogen Displaces Mitochondria in GSD I
In GSD I, the increased glycogen occupies most of the cytoplasm and causes mitochondrial displacement to the cell margin. A lipid vacuole is also present .



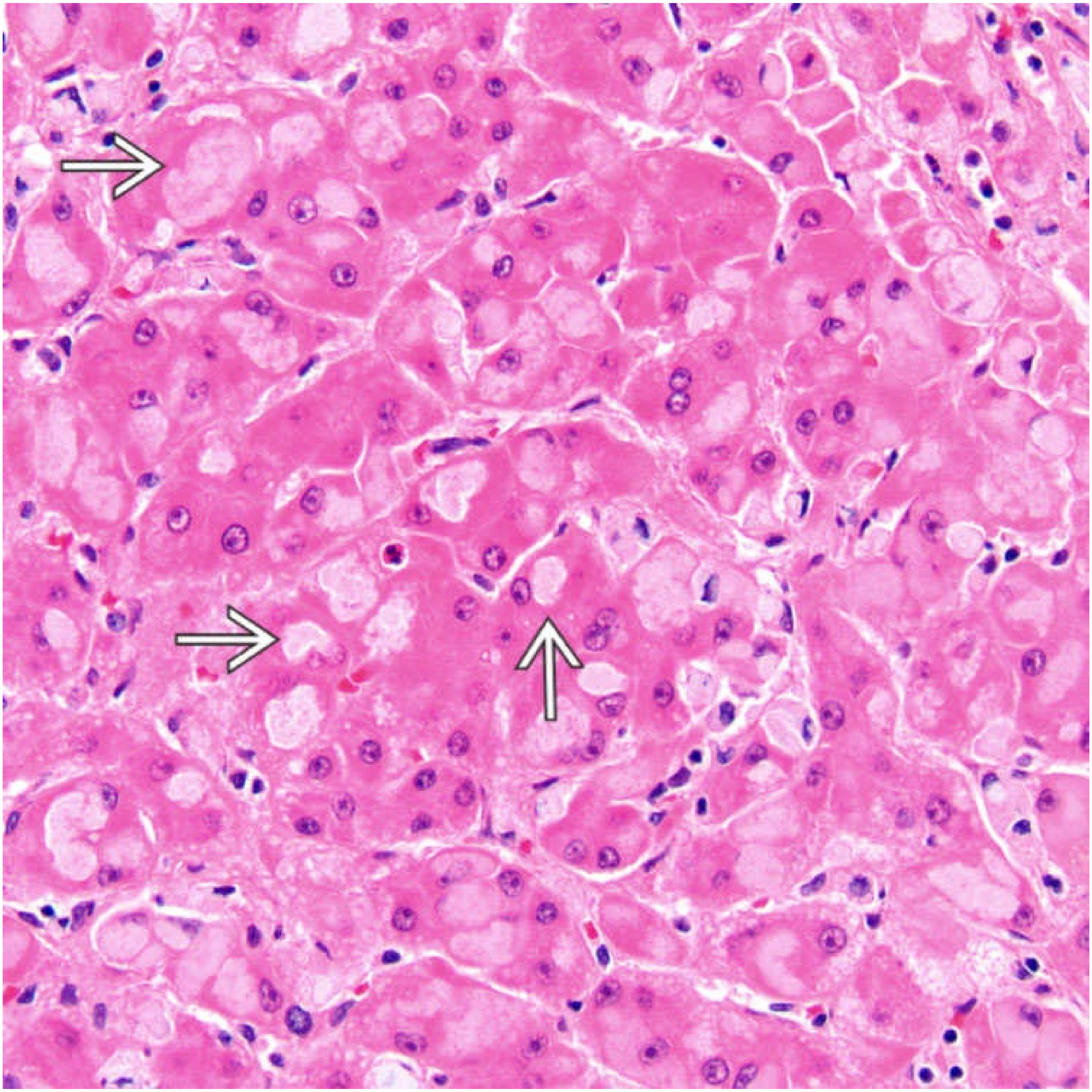
Mosaic Pattern in GSD III
In GSD III, the hepatocytes are arranged in a uniform mosaic pattern similar to GSD I but may reveal less fatty change. This focus has many hepatocytes with intranuclear glycogen, a feature that is more frequently observed in GSD I.



Enlarged Hepatocytes, Fibrosis in GSD III
The hepatocytes are distended with glycogen and create a mosaic architecture that is interrupted by fibrosis in this case of GSD III.

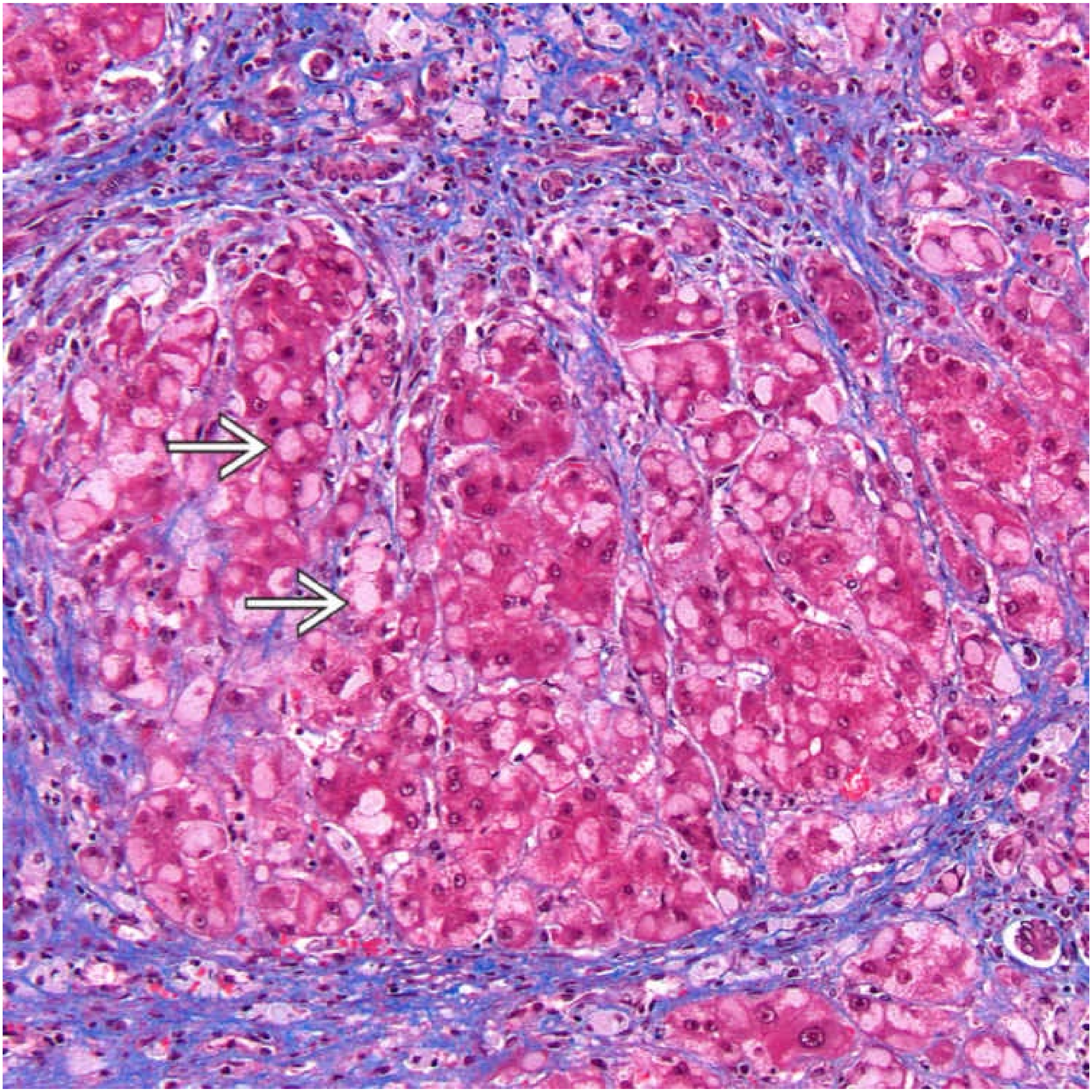


Cirrhosis in GSD III
This needle core biopsy from a patient with GSD III depicts cirrhosis characterized by nodules of hepatocytes partially surrounded by fibrosis.

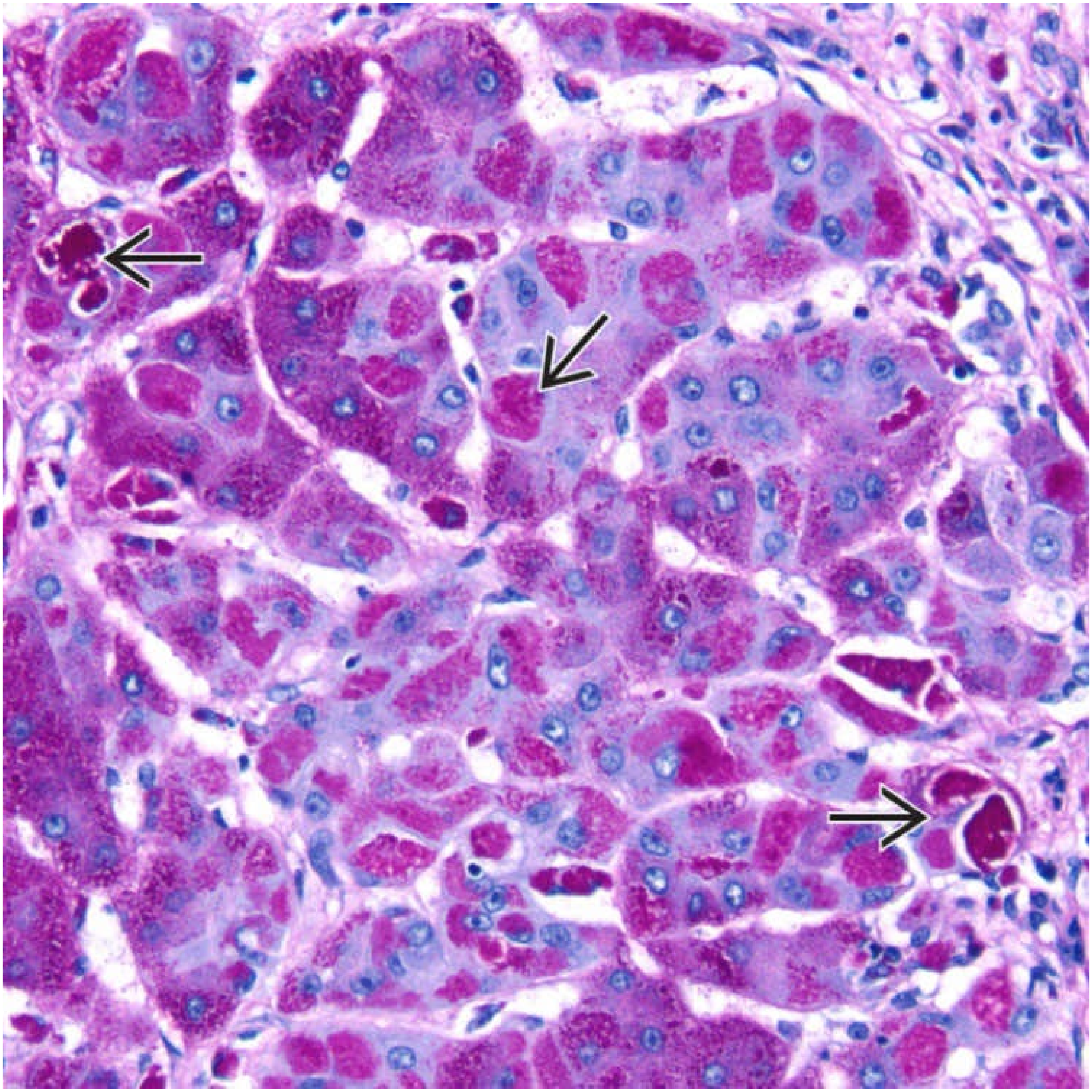


Cytoplasmic Inclusions in GSD IV

GSD IV demonstrates characteristic cytoplasmic inclusions ⇒ within hepatocytes (with H&E stain, by light microscopy) that distinguish it from the other types of GSD. These inclusions are kidney bean-shaped and lightly basophilic.

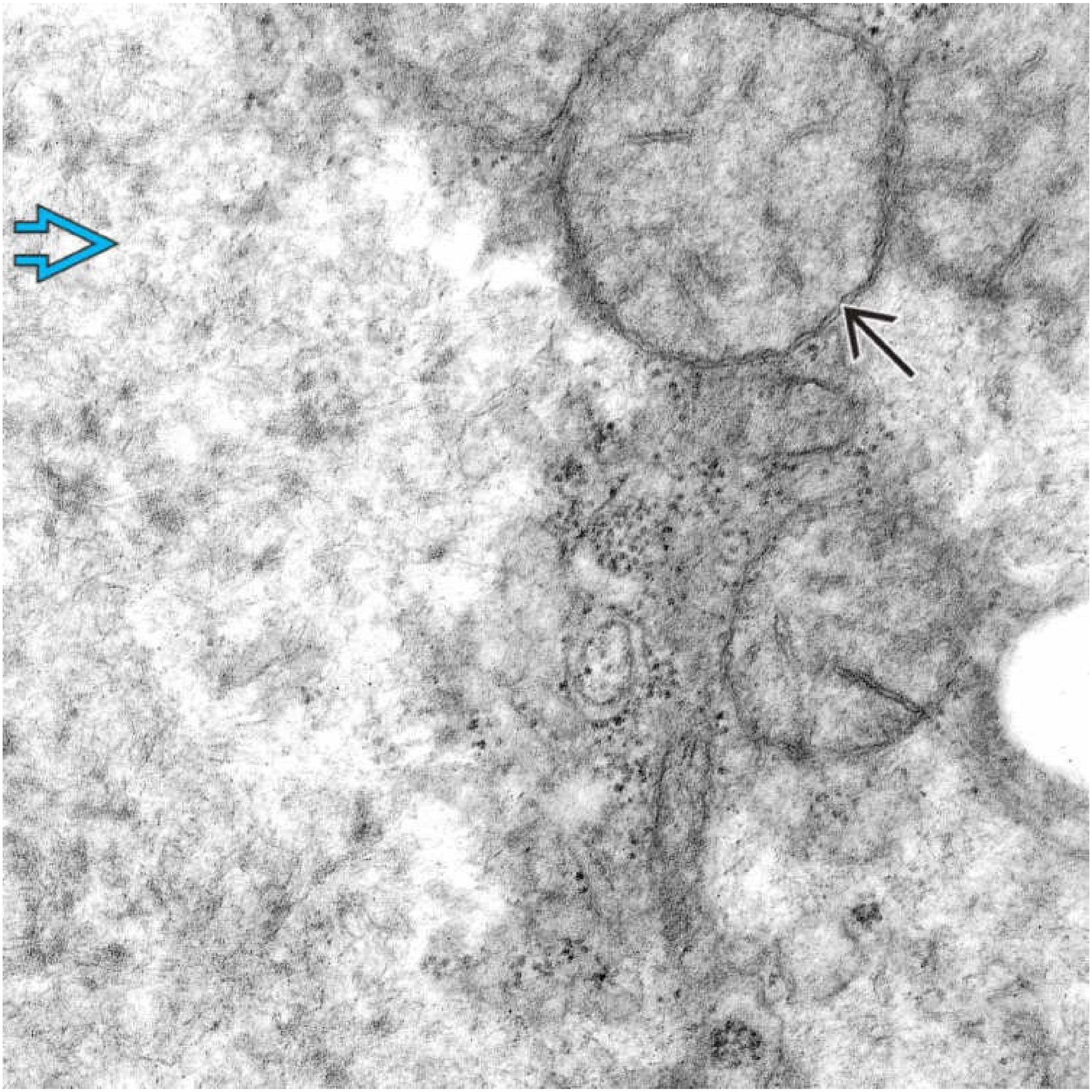


Cirrhosis in GSD IV
Trichrome highlights a small cirrhotic nodule completely surrounded by fibrosis in this case of GSD IV that has evolved into cirrhosis. The cytoplasmic inclusions ⇨ of GSD IV are also apparent.



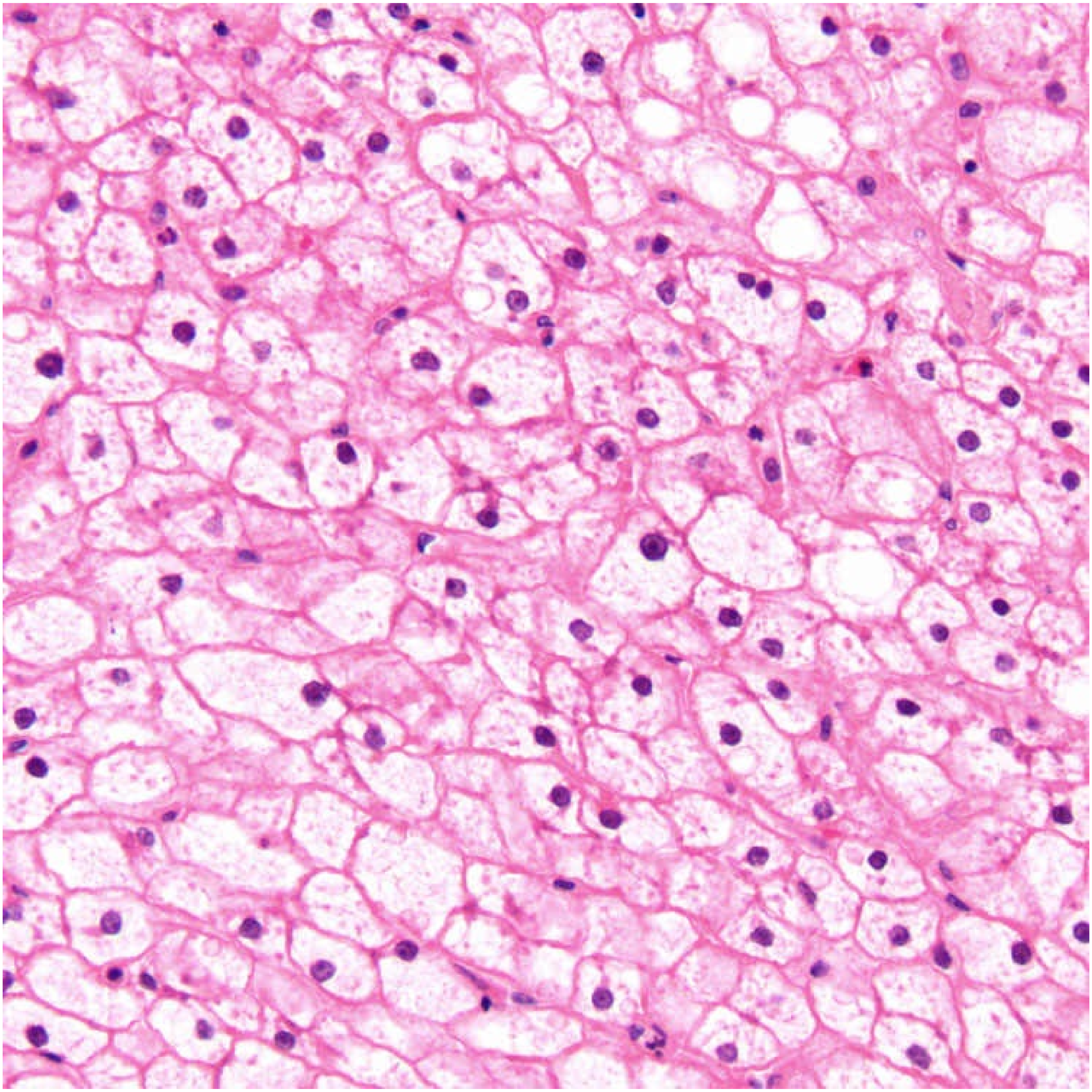
PAS(+) Cytoplasmic Inclusions in GSD IV

The characteristic inclusions → in GSD IV are positive for PAS. These hepatocytes contain both glycogen and amylopectin-like material.

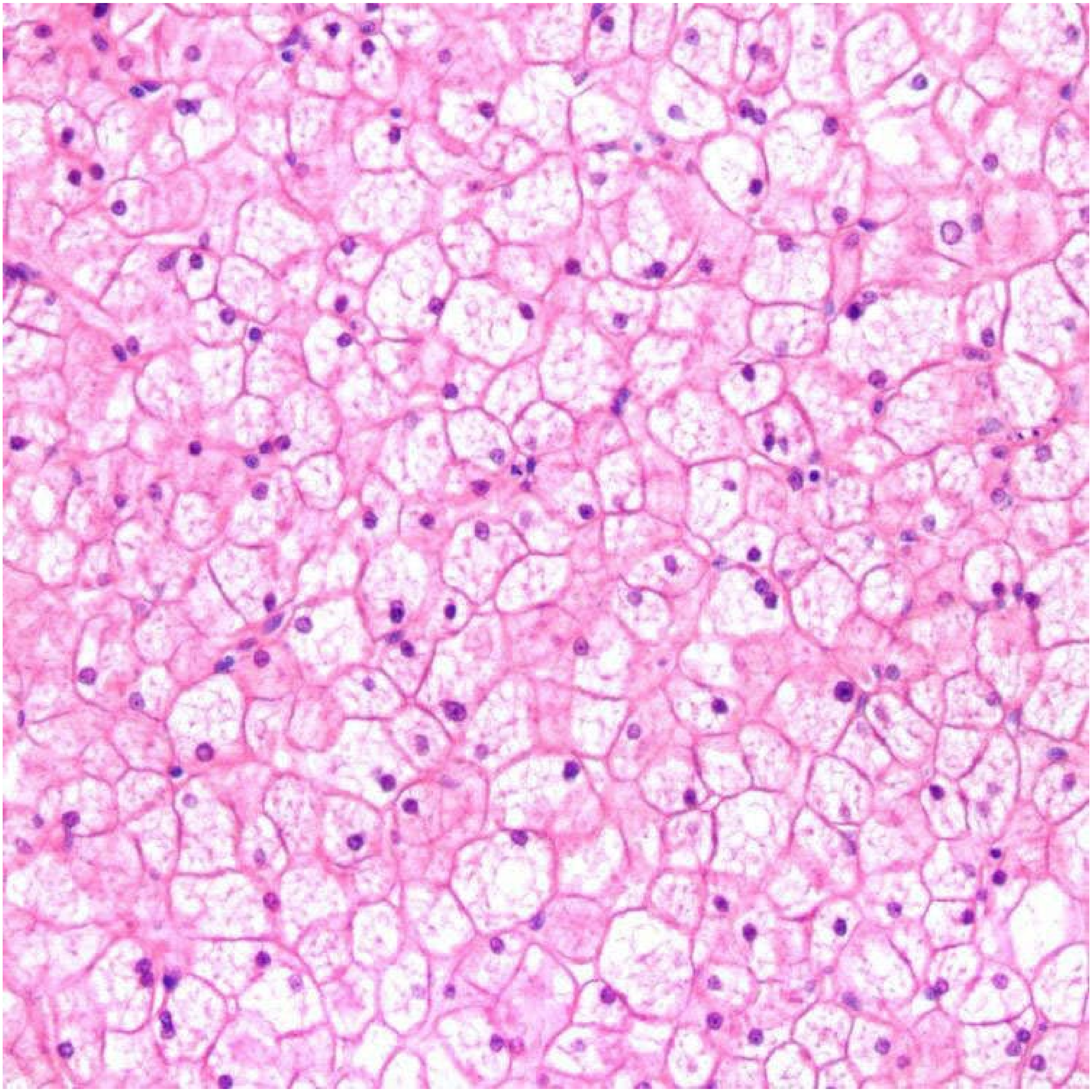


Fibrillary Glycogen in GSD IV

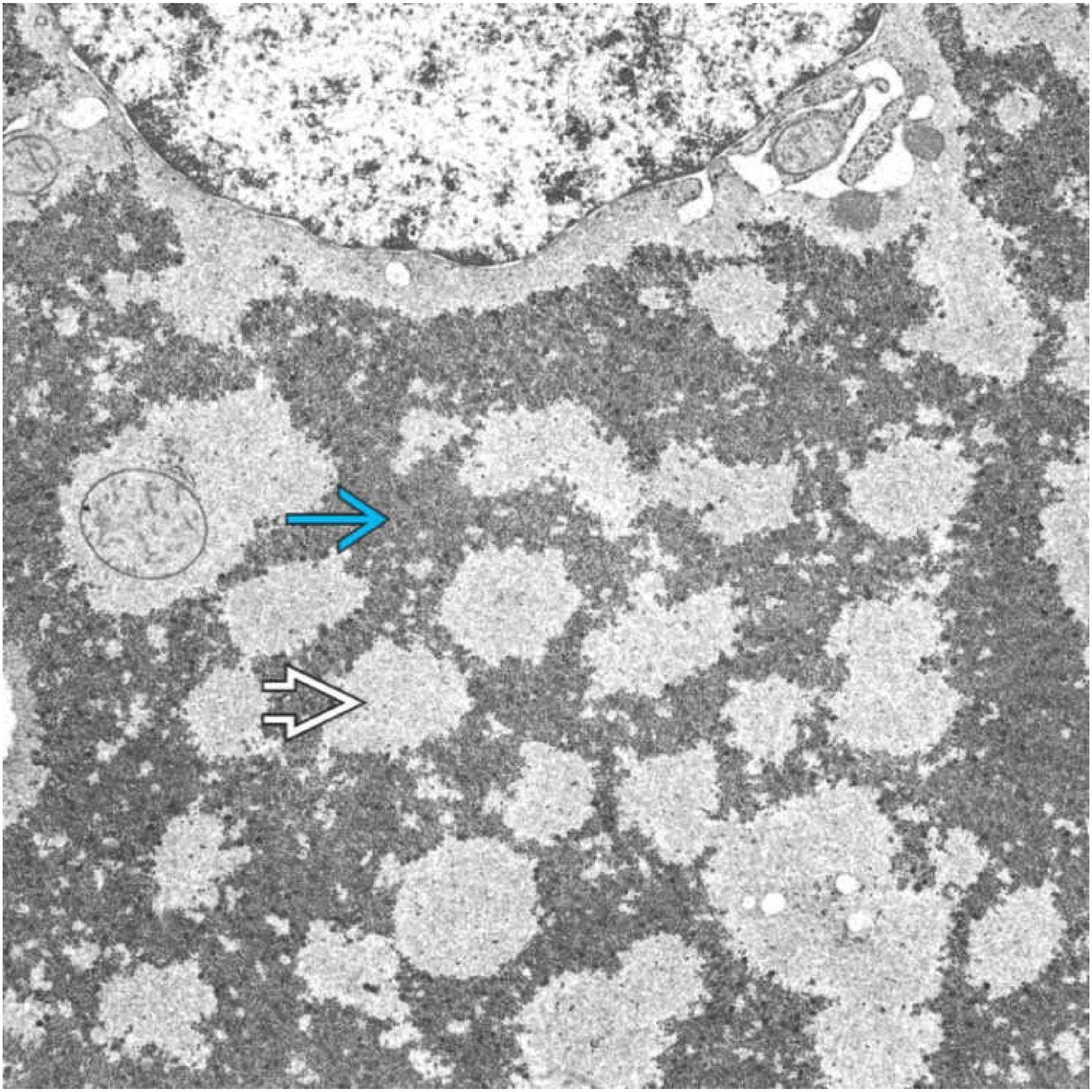
Higher magnification highlights the fibrillary quality of the glycogen ➡ typical of GSD IV and a mitochondria → at the periphery. (Courtesy J. Hicks, MD.)



Irregular, Enlarged Hepatocytes in GSD IX
Unlike the uniform hepatocytes previously noted in GSD I and III, those in GSD IX are irregular in size and only rarely demonstrate nuclear glycogen.

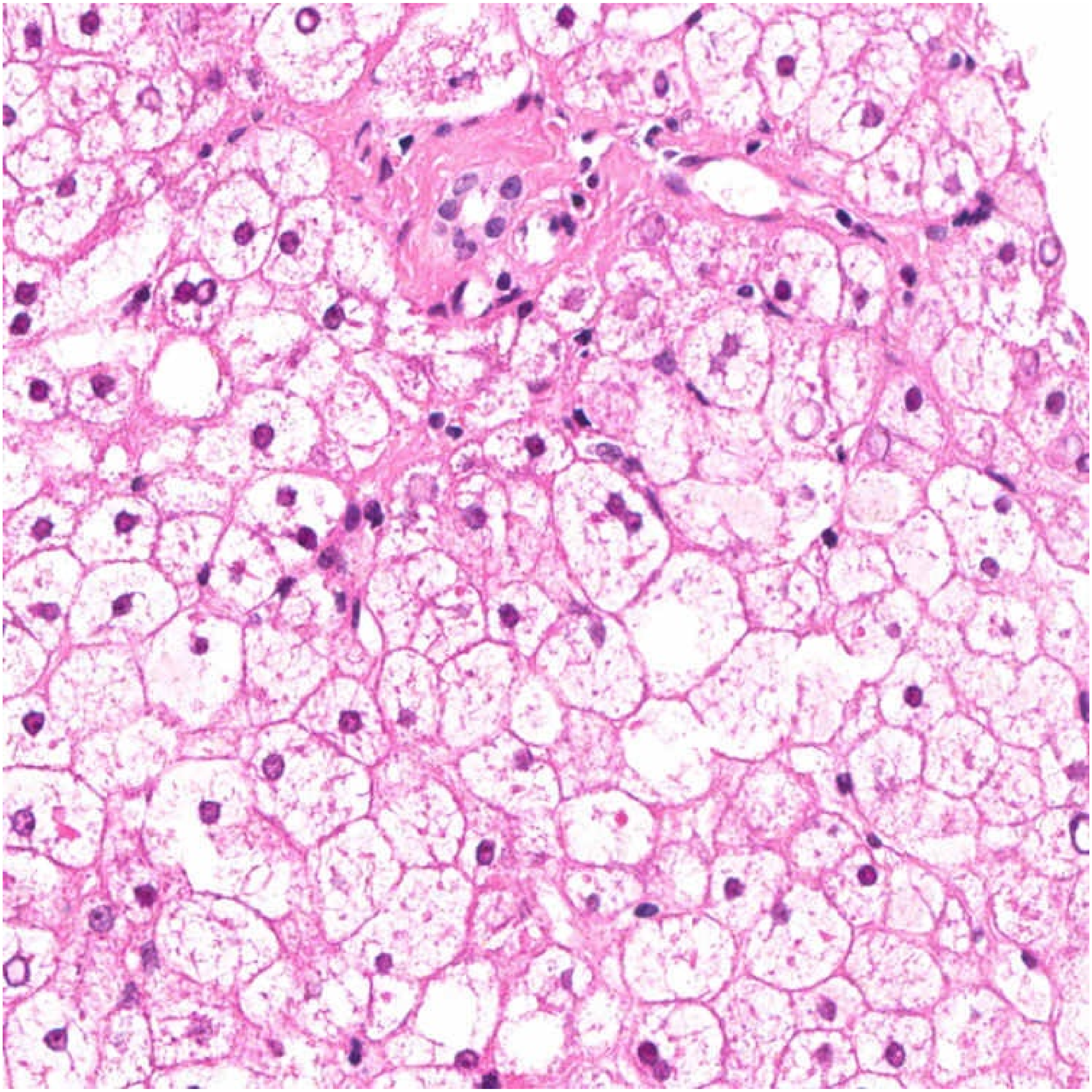


Enlarged Hepatocytes and Compressed Sinusoids in GSD IX
This example of GSD IX shows hepatocyte enlargement, prominent cell membranes, and compression of sinusoids.

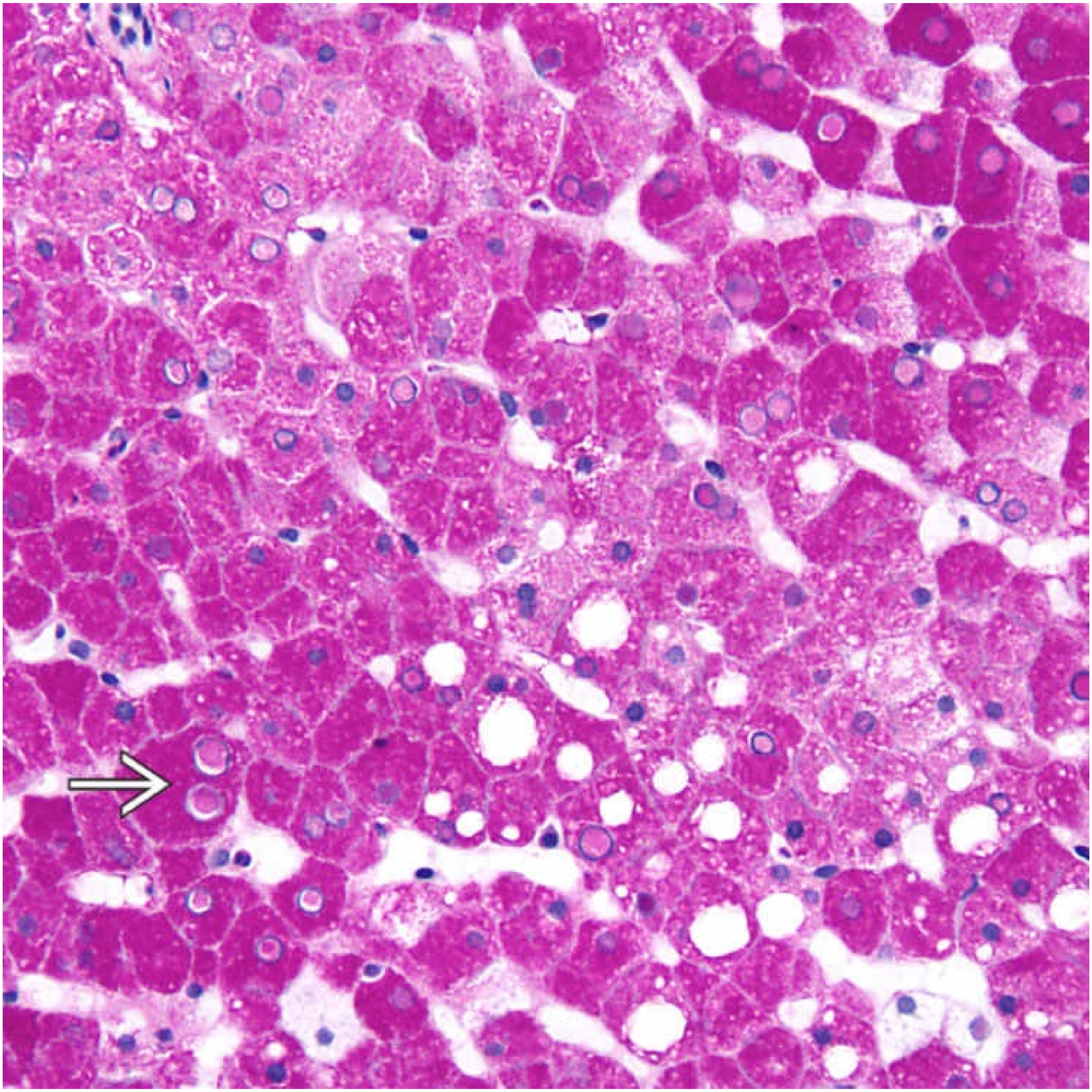


Starry-Sky Appearance of GSD IX

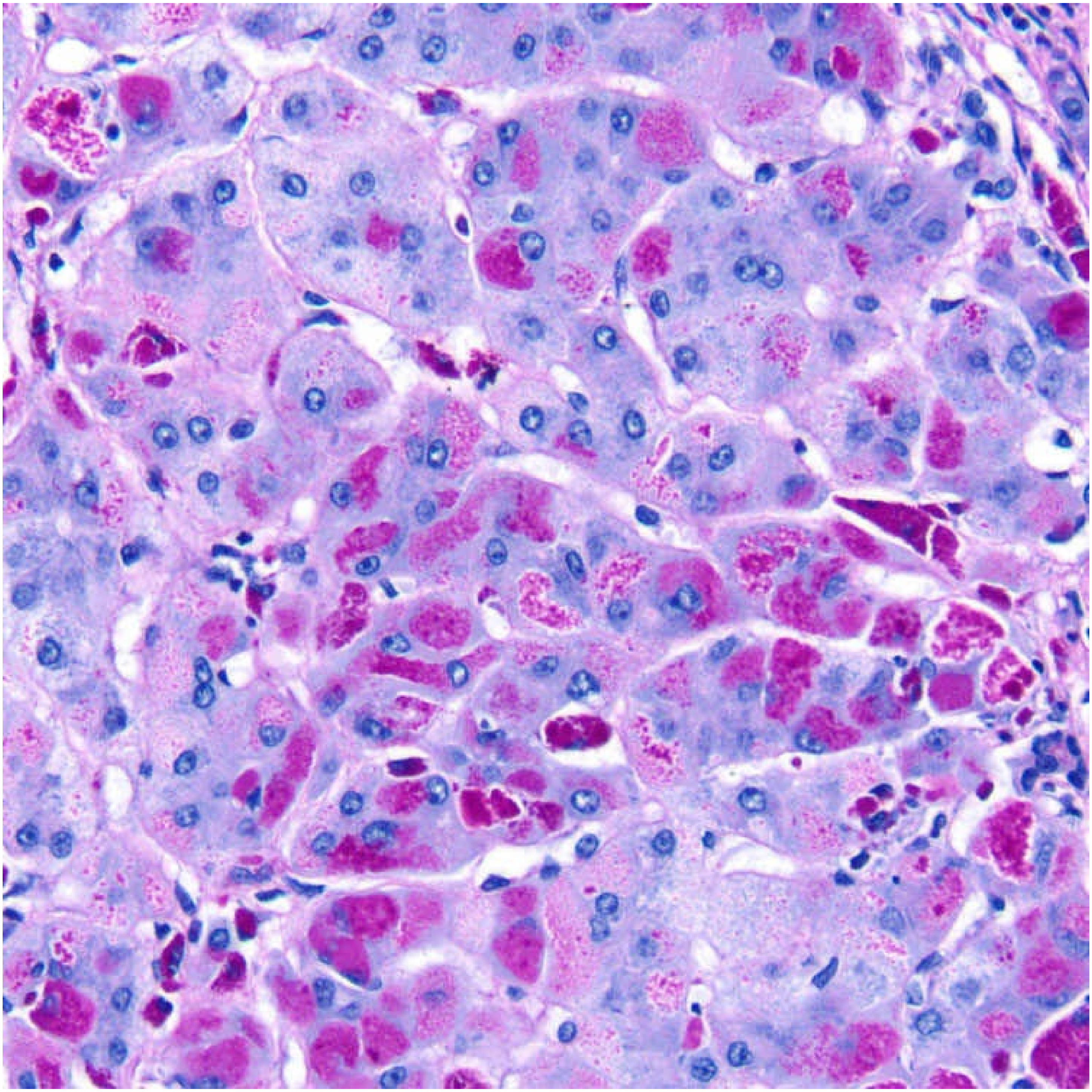
GSD IX at higher magnification highlights the starry-sky appearance. This results from patchy zones of glycogen → (dark areas) alternating with organelle-free zones ⇨ (pale gray areas).



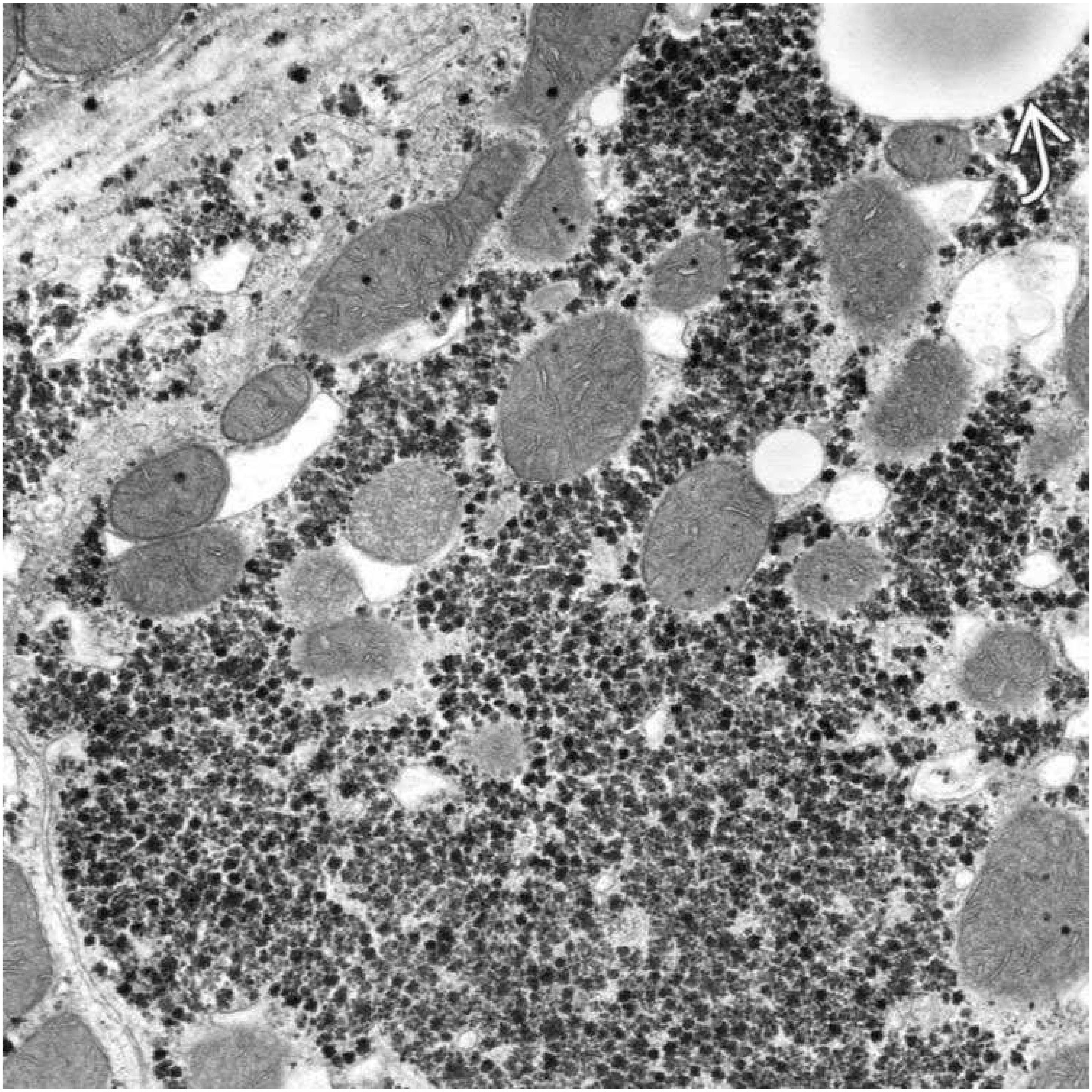
Glycogenic Hepatopathy Mimics GSD
Glycogenic hepatopathy mimics GSD histologically with enlarged hepatocytes and prominent cell borders. However, it has a distinct clinical picture from GSD, occurring in patients with poorly controlled type 1 diabetes mellitus.



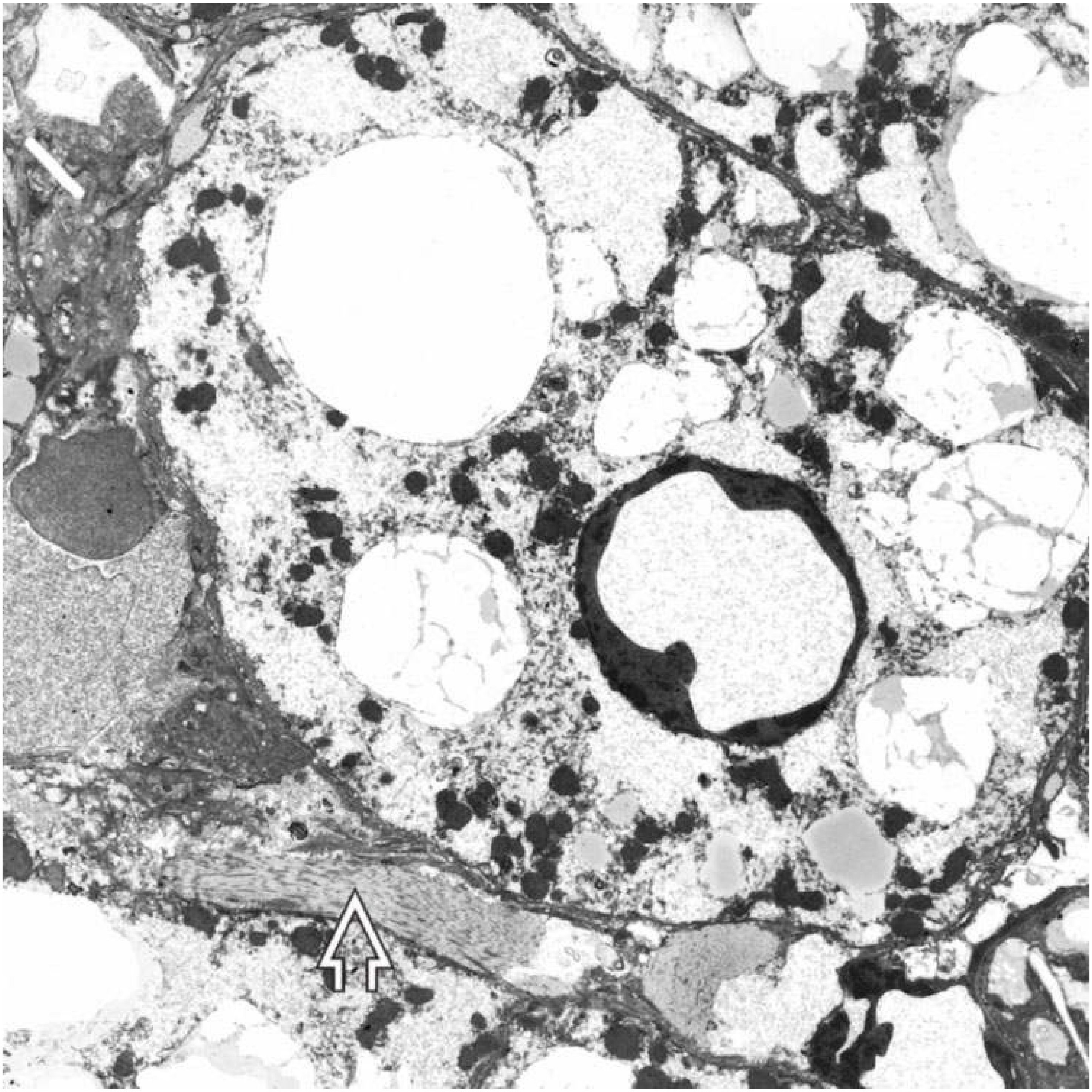
This case of GSD III stained with PAS highlights diffuse cytoplasmic glycogen in hepatocytes and occasional intranuclear glycogen ⇒. These features can be observed in most hepatic GSD, except in types 0 and IV.



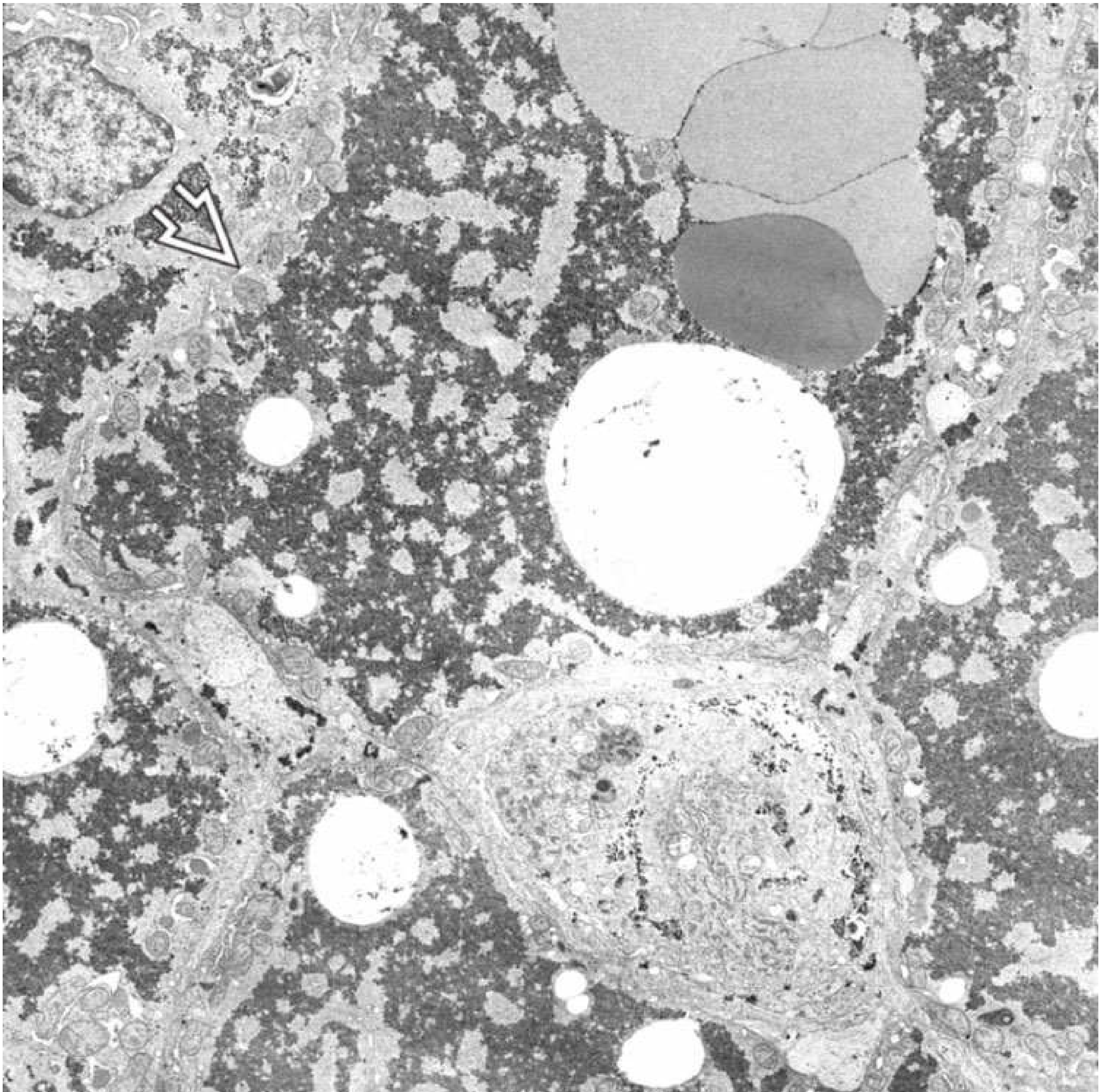
The amylopectin-like material that coexists with glycogen in the cytoplasm of hepatocytes results in the inclusions unique to GSD IV. Some positive staining with PAS-D is retained in the amylopectin-like material.



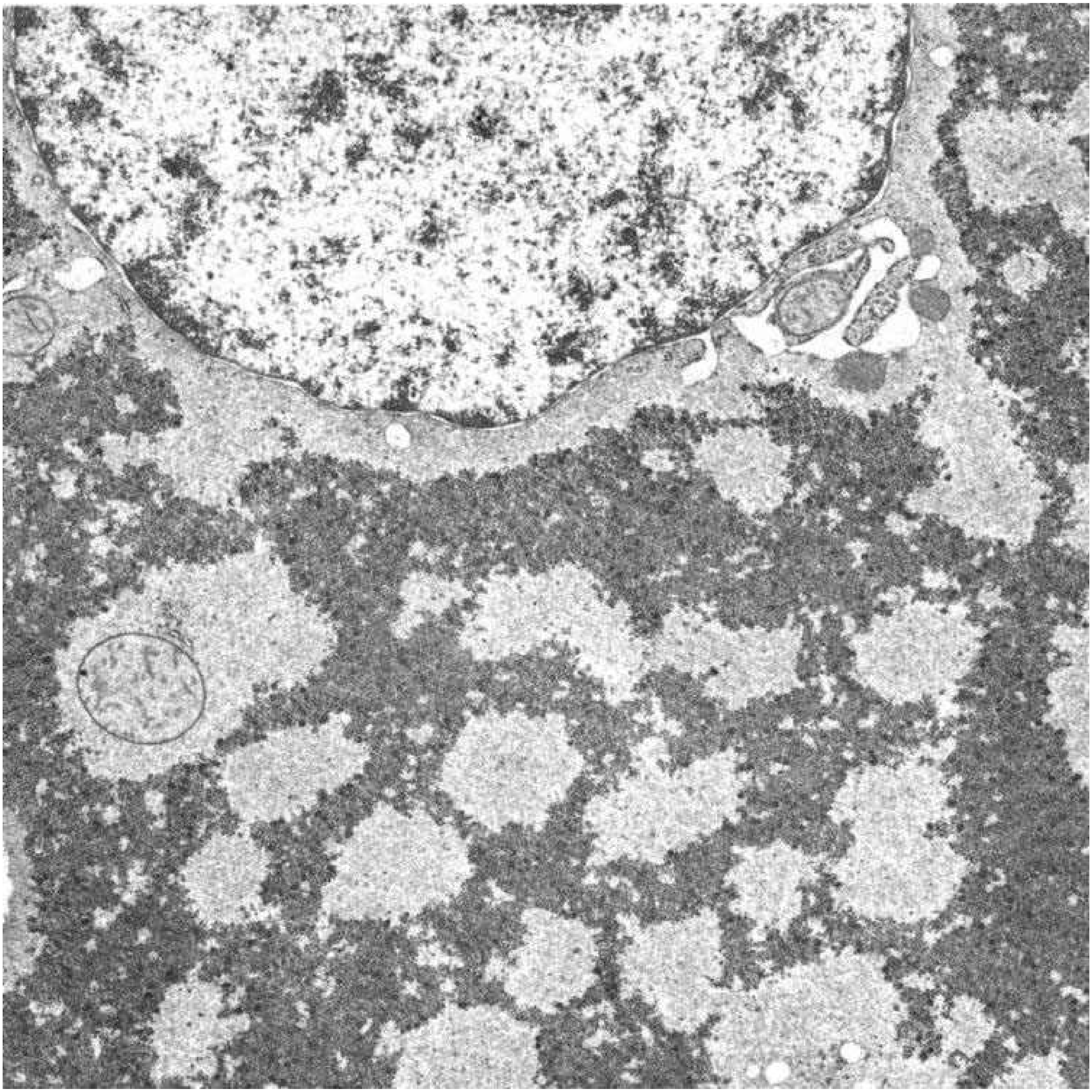
GSD I is shown with increased glycogen that occupies most of the cytoplasm and mitochondrial disbursement to the cell margin. A lipid vacuole is also present.



A hepatocyte from GSD III reveals cytoplasmic and intranuclear glycogen along with cytoplasmic lipid droplets. Fibrosis is characterized by the presence of collagen bundles ⇨ .



GSD IX at low magnification depicts displacement of hepatocellular mitochondria ⇨ by cytoplasmic glycogen and lipid. The mitochondria are displaced to the periphery of the cytoplasm in these hepatocytes.



GSD IX at higher magnification highlights the starry-sky appearance. This results from patchy zones of glycogen (dark areas) alternating with organelle-free zones (pale gray areas).

SELECTED REFERENCES

1. Bhattacharya, K. Investigation and management of the hepatic glycogen storage diseases. *Transl Pediatr*. 2015; 4(3):240–248.
2. Burda, P, et al. Hepatic glycogen storage disorders: what have we learned in recent years? *Curr Opin Clin Nutr Metab Care*. 2015; 18(4):415–421.
4. Heller, S, et al. Nutritional therapy for glycogen storage diseases. *J Pediatr Gastroenterol Nutr*. 2008; 47(Suppl 1):S15–S21.
5. Demo, E, et al. Glycogen storage disease type III-hepatocellular carcinoma a long-term complication? *J Hepatol*. 2007; 46(3):492–498.

6. Ozen, H. Glycogen storage diseases: new perspectives. *World J Gastroenterol*. 2007; 13(18):2541–2553.

3. Ovchinsky, N, et al. Liver biopsy in modern clinical practice: a pediatric point-of-view. *Adv Anat Pathol*. 2012; 19(4):250–262.
7. Torbenson, M, et al. Glycogenic hepatopathy: an underrecognized hepatic complication of diabetes mellitus. *Am J Surg Pathol*. 2006; 30(4):508–513.
8. Wisell, J, et al. Glycogen pseudoground glass change in hepatocytes. *Am J Surg Pathol*. 2006; 30(9):1085–1090.
9. Miles, L, et al. Hepatocyte glycogen accumulation in patients undergoing dietary management of urea cycle defects mimics storage disease. *J Pediatr Gastroenterol Nutr*. 2005; 40(4):471–476.
10. Laberge, AM, et al. Long-term follow-up of a new case of liver glycogen synthase deficiency. *Am J Med Genet A*. 2003; 120A(1):19–22.
11. Wolfsdorf, JI, et al. Glycogen storage diseases. Phenotypic, genetic, and biochemical characteristics, and therapy. *Endocrinol Metab Clin North Am*. 1999; 28(4):801–823.
12. Bao, Y, et al. Hepatic and neuromuscular forms of glycogen storage disease type IV caused by mutations in the same glycogen-branching enzyme gene. *J Clin Invest*. 1996; 97(4):941–948.
13. Jevon, GP, et al. Reliability of histological criteria in glycogen storage disease of the liver. *Pediatr Pathol*. 1994; 14(4):709–721.
14. Bianchi, L. Glycogen storage disease I and hepatocellular tumours. *Eur J Pediatr*. 1993; 152(Suppl 1):S63–S70.
15. Phillips, MJ, et alThe liver. An Atlas and Text of Ultrastructural Pathology. New York: Raven Press, 1987.
16. McAdams, AJ, et al. Glycogen storage disease, types I to X: criteria for morphologic diagnosis. *Hum Pathol*. 1974; 5(4):463–487.

Tyrosinemia

KEY FACTS

Terminology

• Synonym: Tyrosinemia, type I

Etiology/Pathogenesis

• Mutations in fumarylacetoacetate hydrolase gene on 15q23-q25
• Fumarylacetoacetate hydroxylase deficiency
• Autosomal recessive inheritance

Clinical Issues

• Highly variable symptoms
• Elevated plasma and urine succinylacetone
• Many patients have renal tubular dysfunction
• 15-37% risk of developing hepatocellular carcinoma
• Prior to early detection, > 90% mortality before 2 years of age
• Liver transplantation is treatment of choice for medical treatment failures

Microscopic

• Variable fatty change and cholestasis
• Pericellular and periportal fibrosis to cirrhosis
• Acute form with massive hepatocyte necrosis

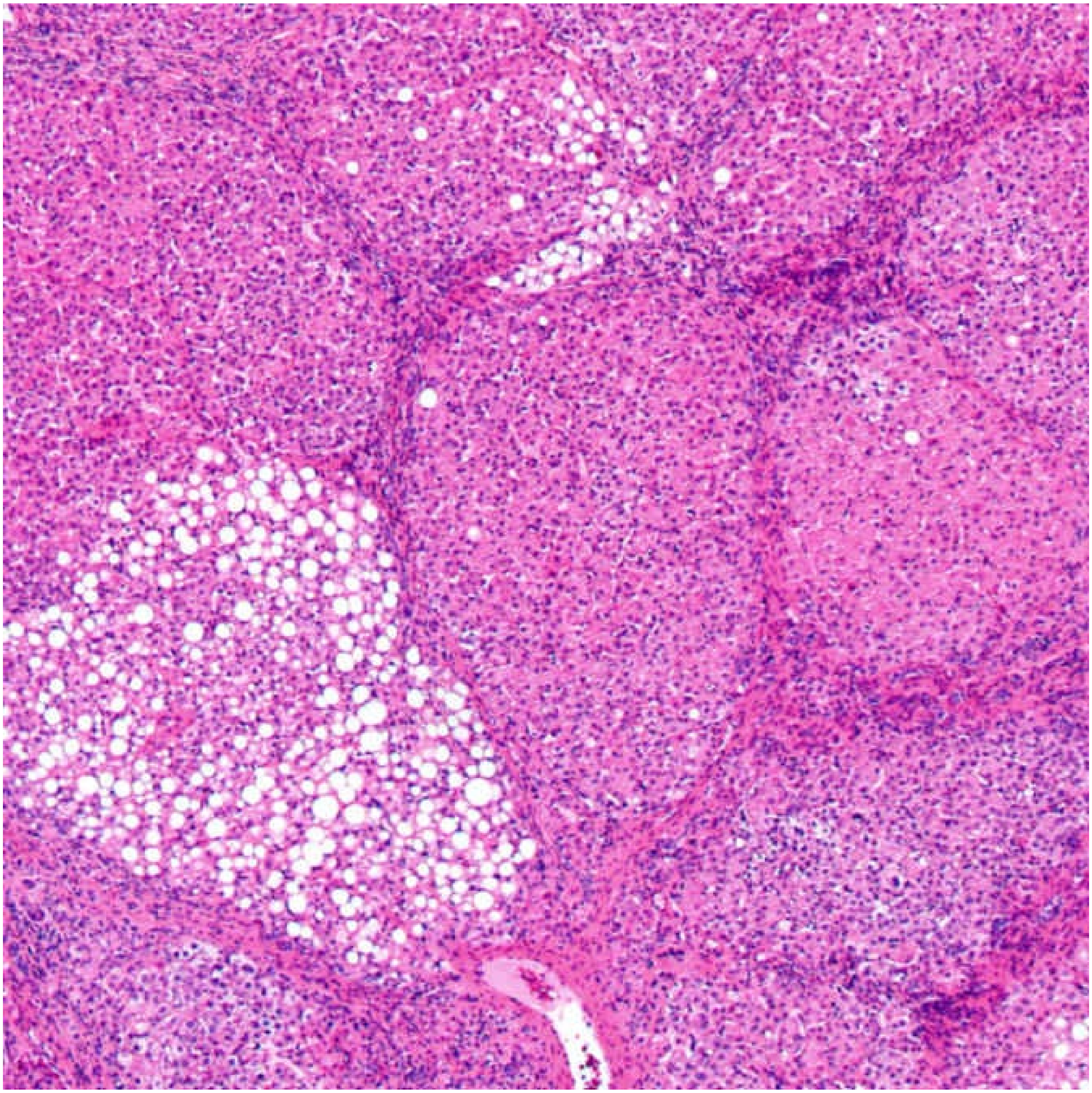
Top Differential Diagnoses

• Galactosemia
  ○ Distinguished clinically
• Hereditary fructose intolerance
  ○ Distinct ultrastructural features

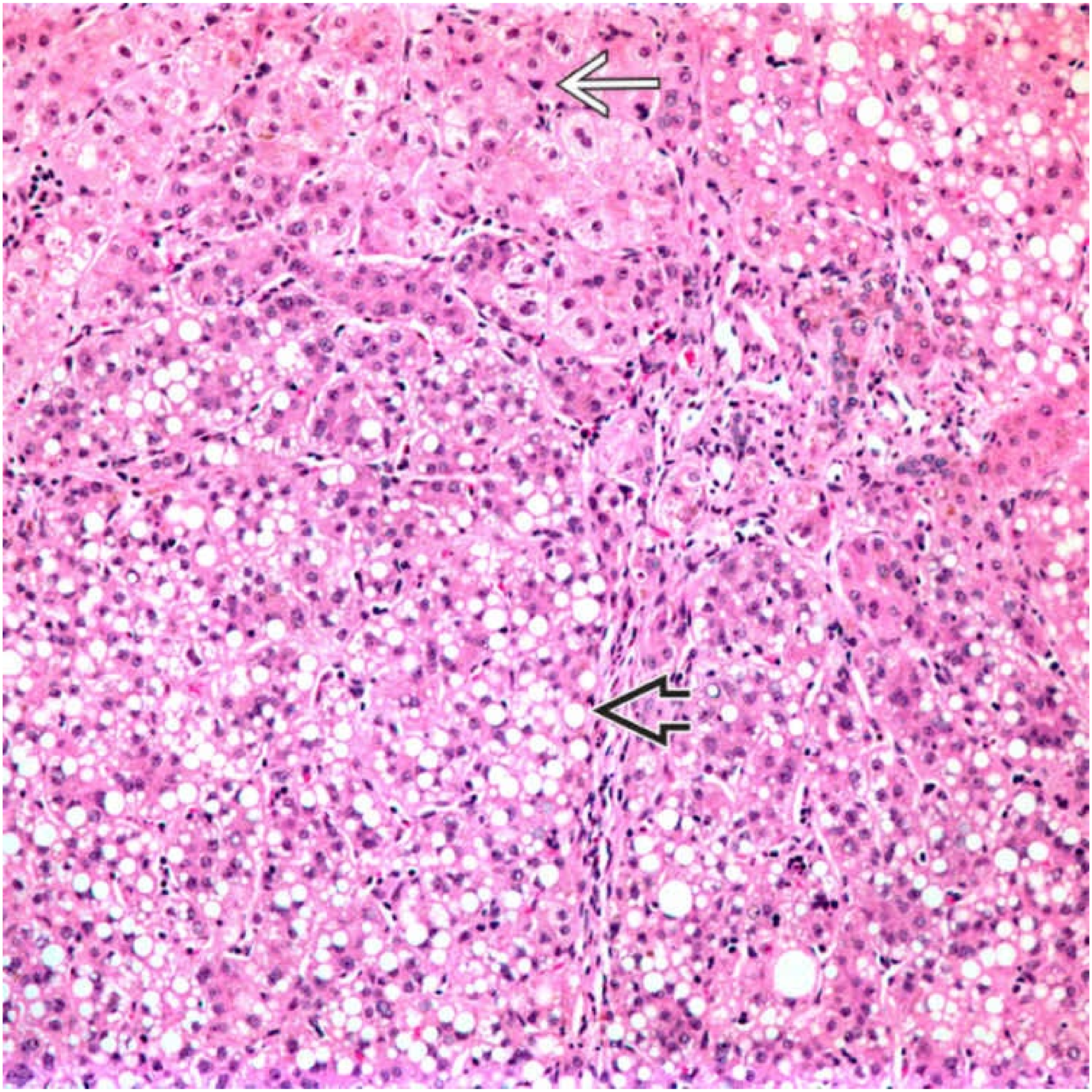
• Neonatal hemochromatosis

Diagnostic Checklist

• Fibrosis with variable amounts of steatosis and cholestasis; requires clinical correlation
• High risk of hepatocellular carcinoma

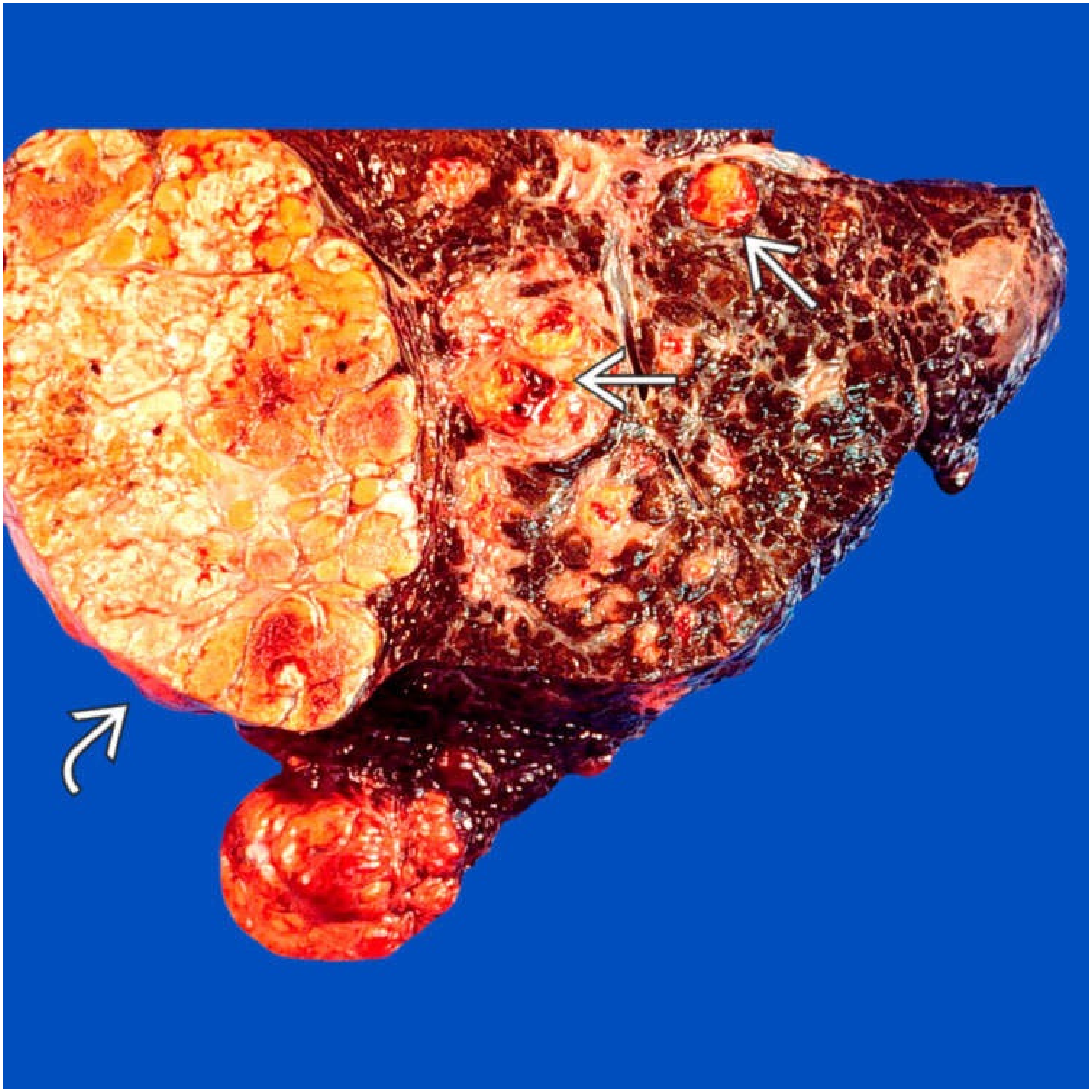


Micronodular Cirrhosis and Fatty Change
This liver with micronodular cirrhosis demonstrates focal areas of large droplet fatty change in some nodules. The fatty change in tyrosinemia is often patchy.

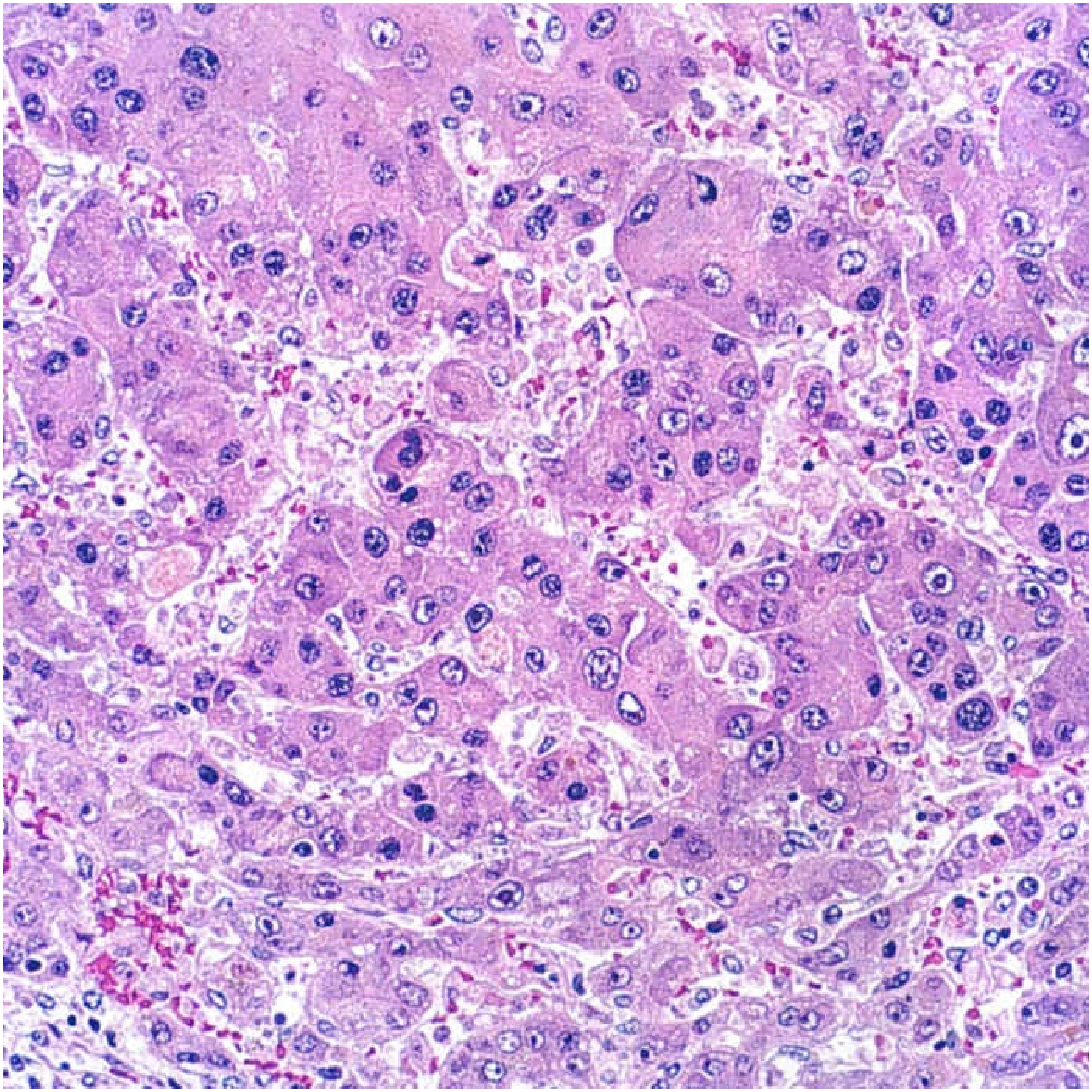


Dysplastic Nodule

A dysplastic nodule in a patient with tyrosinemia displays both small cell change and widened plate architecture. Note the adjacent normal liver. (Courtesy M. J. Finegold, MD.)



Hepatocellular Carcinoma and Cirrhosis
Gross photograph of an explanted cirrhotic liver from a 1.5 year old depicts a 7.5-cm multinodular, yellow mass as well as smaller nodules. (Courtesy M. J. Finegold, MD.)


Hepatocellular Carcinoma
Histology of a mass from an explanted cirrhotic liver is shown. Note the abnormal plate architecture and enlarged hyperchromatic nuclei typical of hepatocellular carcinoma. (Courtesy M. J. Finegold, MD.)

TERMINOLOGY

Abbreviations

- Fumarylacetoacetate hydroxylase (FAH) deficiency

Synonyms

- Tyrosinemia, type I
- Hereditary tyrosinemia
- Hepatorenal tyrosinemia

Definitions

- Inborn error of metabolism in tyrosine catabolism pathway
  - Deficiency of FAH
  - Results in cirrhosis and hepatocellular carcinoma early in life

ETIOLOGY/PATHOGENESIS

Molecular Basis

- Fumarylacetoacetate hydrolase deficiency due to 15q23-q25 gene mutations
  - Accumulation of toxic and mutagenic metabolites, maleylacetoacetate, and fumarylacetoacetate
  - Excretion of secondary metabolite succinylacetone
- Autosomal recessive inheritance

CLINICAL ISSUES

Epidemiology

- Incidence
  - 1/100,000 to 1/120,000 worldwide; higher in Scandinavia and Quebec

Presentation

- Highly variable symptoms
  - Acute liver failure with hepatic synthetic dysfunction
  - Renal tubular dysfunction
  - Hypophosphatemic rickets
  - Neurologic crises with episodic paralysis and peripheral neuropathy
  - Positive newborn screening test

Laboratory Tests

- Elevated plasma and urine succinylacetone
- Elevated urinary 5-aminolevulinic acid
- Tyrosinemia and methioninemia on urinary amino acid analysis
- Elevated serum α-fetoprotein
- Decreased fumarylacetoacetate hydrolase enzymatic activity in cultured amniotic cells, fibroblasts, or liver

Natural History

- Prior to early detection, > 90% mortality before 2 years of age
- Progression of fibrosis to cirrhosis
- 15-37% risk of developing hepatocellular carcinoma

Treatment

- Dietary restriction of phenylalanine, tyrosine, and methionine
  - Normalizes plasma amino acids and improves acute symptoms only
- Nitisinone inhibits 2nd enzymatic step in tyrosine catabolic pathway
  - Early therapy reduces incidence of hepatocellular carcinoma
- Eventual need for orthotopic liver transplantation

Prognosis

- Good if detected early prior to development of hepatocellular carcinoma and transplanted
- If dietary treatment only, > 90% mortality by 12 years of age

MACROSCOPIC

General Features

- Cirrhosis, either macronodular, micronodular, or mixed

MICROSCOPIC

Histologic Features

- Cholestasis (variable amounts) and pseudoacinar transformation
- Patchy large or small droplet fatty change
- Hemosiderosis
- Pericellular and periportal fibrosis that may progress to cirrhosis
- Acute form with massive hepatocyte necrosis

DIFFERENTIAL DIAGNOSIS

Other Metabolic Diseases

- Galactosemia
  - Similar histologic and ultrastructural findings
    - Requires clinical distinction
- Hereditary fructose intolerance
  - Histologically similar but ultrastructural changes are nearly diagnostic
    - Fructose holes: Ovoid to irregular lucent, partially membrane-bound areas of cytoplasm; up to 2 μm
    - Distinctive concentric arrays of endoplasmic reticulum with central rarefaction and glycogen particles

Neonatal Hemochromatosis

- Both can have increased iron stores in liver
- Neonatal hemochromatosis characterized by systemic iron deposition

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- High risk of hepatocellular carcinoma

Pathologic Interpretation Pearls

- Fibrosis with variable amounts of steatosis and cholestasis
- Nonspecific histology requires clinical correlation to make diagnosis

SELECTED REFERENCES

1. de Laet, C, et al. Recommendations for the management of tyrosinaemia type 1. *Orphanet J Rare Dis*. 2013; 8:8.
2. Dehner, LP, et al. Hereditary tyrosinemia type I (chronic form): pathologic findings in the liver. *Hum Pathol*. 1989; 20(2):149–158.
3. Weinberg, AG, et al. The occurrence of hepatoma in the chronic form of hereditary tyrosinemia. *J Pediatr*. 1976; 88(3):434–438.

Niemann-Pick Disease

KEY FACTS

Terminology

- Lysosomal storage disease resulting from defects in lysosomal function
  - Autosomal recessive

Classification

- Types A and B characterized by acid sphingomyelinase deficiency
- Types C and D harbor cholesterol metabolism defect

Etiology/Pathogenesis

- Inherited lysosomal hydrolase deficiency leads to accumulation of sphingolipid substrate in lysosomes
- Types A and B: Deficient acid sphingomyelinase activity results in sphingomyelin accumulation
- Types C and D: Cholesterol metabolism defect leads to accumulation of cholesterol and sphingomyelin

Clinical Issues

- Estimated 0.5-1.0 cases in 100,000 newborns
- Hepatosplenomegaly with variable neurodegenerative course
- No specific treatment available

Microscopic

- Spotty accumulation of enlarged histiocytes with cytoplasmic inclusions in hepatic lobules and portal tracts
- Histiocyte inclusions are rounded and of fairly uniform size, imparting foamy appearance to cytoplasm

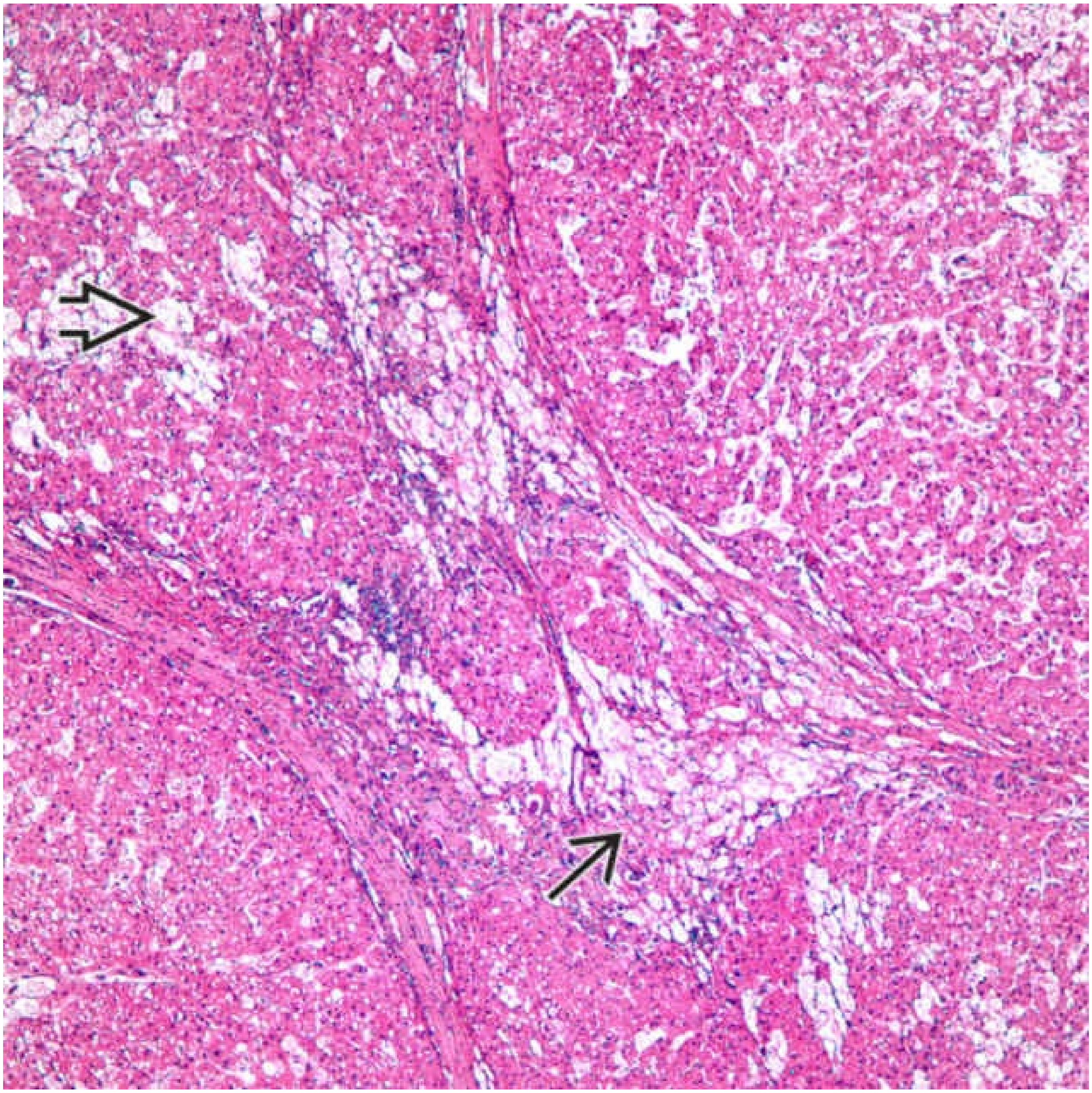
Ancillary Tests

- Electron microscopy shows electron-opaque, concentrically laminated inclusions within histiocyte

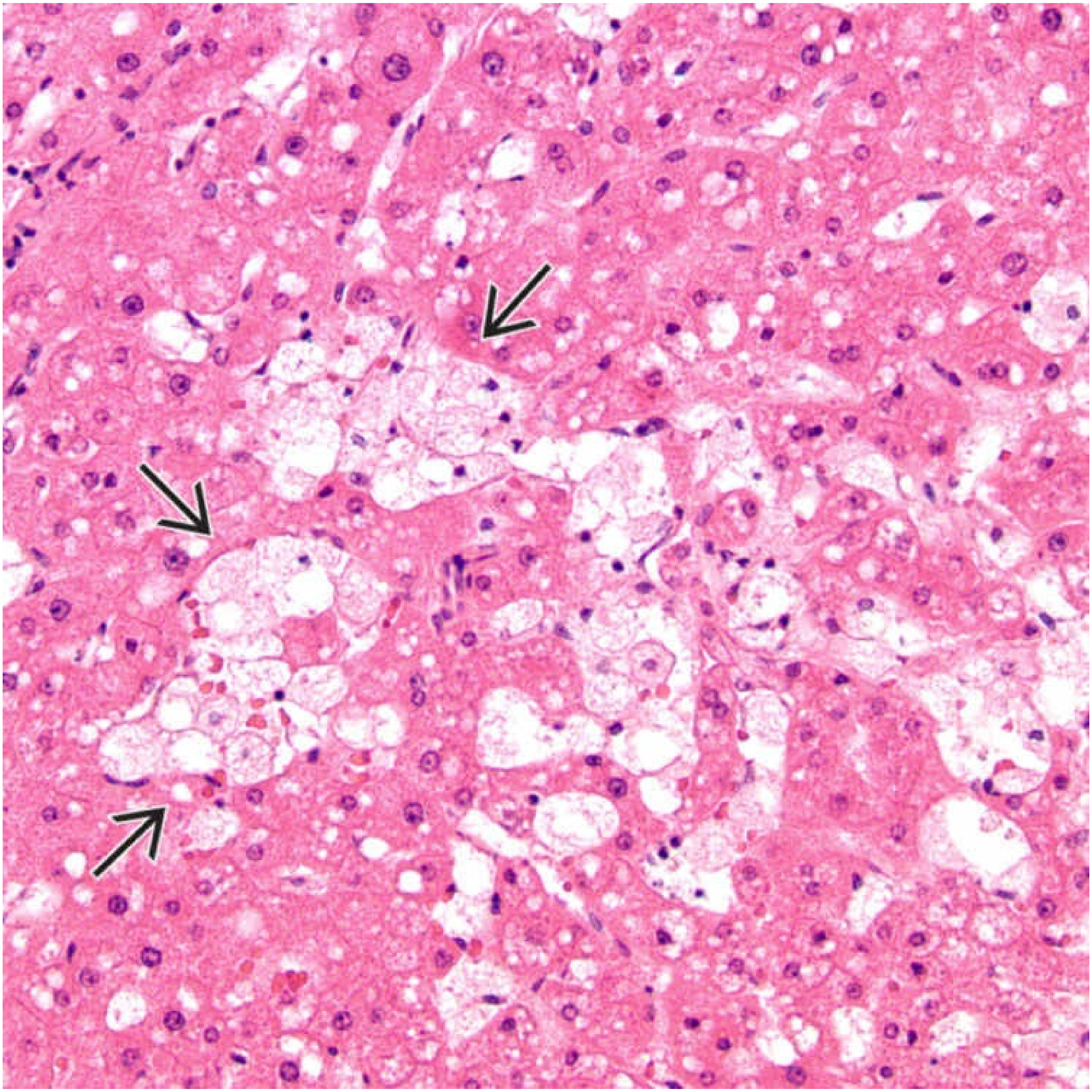
cytoplasm

Top Differential Diagnoses

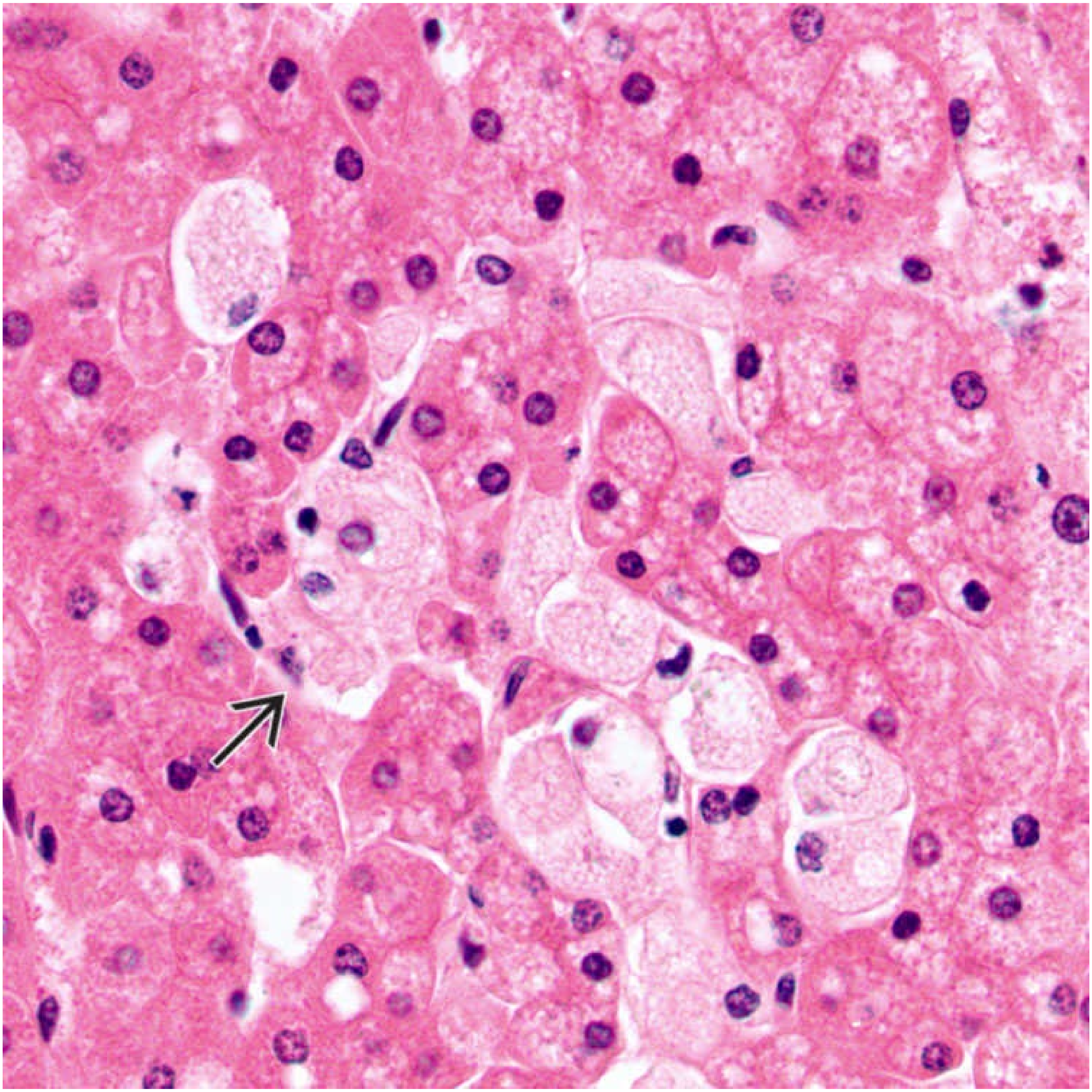
• Gaucher disease: Gaucher cells have striated, fibrillary cytoplasmic inclusions within histiocytes



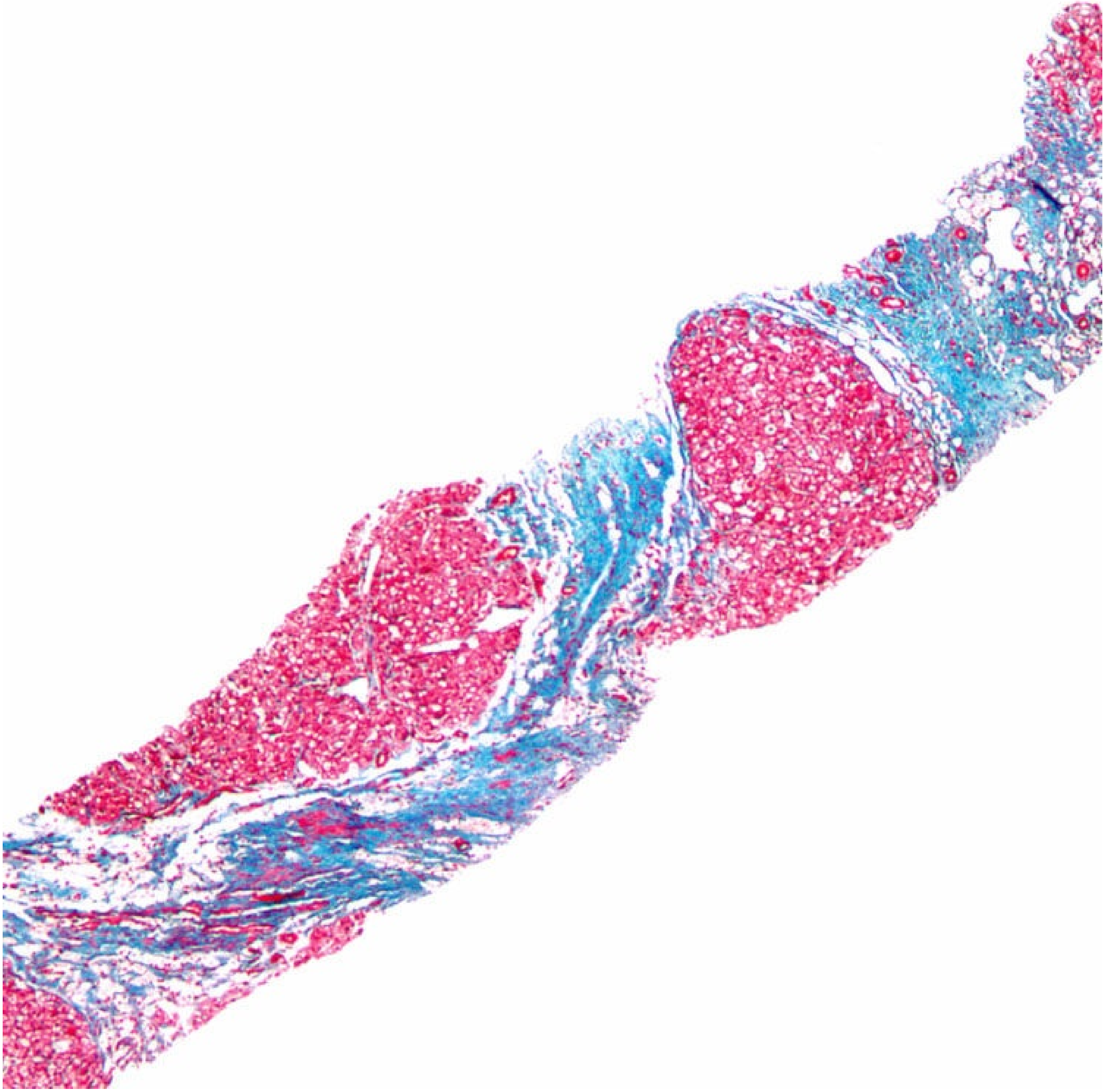
Niemann-Pick Disease in Liver
In this explanted liver, the pale-staining Niemann-Pick cells are evident both within cirrhotic nodules ➩ and in the fibrous septa → .



Niemann-Pick Cells Between Hepatocytes
Niemann-Pick cells are pale histiocytic cells with foamy cytoplasm → that accumulate between hepatocyte cords within the lobular hepatic parenchyma.



Foamy Cytoplasm in Niemann-Pick Cells
Niemann-Pick cells → are pale-staining, large histocytes with amphophilic, foamy, and vacuolated cytoplasmic inclusions. These cells are distinct from the more deeply eosinophilic hepatocytes.



Cirrhosis in Niemann-Pick Disease
Niemann-Pick disease can cause ongoing liver fibrosis with progression to cirrhosis, and subsequent complications of end-stage liver disease.

TERMINOLOGY

Abbreviations

- Niemann-Pick disease (NPD)

Synonyms

- Sphingomyelin-cholesterol lipidosis

Definitions

- Lysosomal storage disease resulting from defects in lysosomal function
  - Disease subtypes
  - Types A and B: Acid sphingomyelinase deficiency
  - Types C and D: Cholesterol metabolism defect

ETIOLOGY/PATHOGENESIS

Enzyme Deficiency

- Inherited lysosomal hydrolase deficiency leads to lysosomal accumulation of sphingolipid substrate

Mode of Inheritance

- Autosomal recessive

Disease Subtypes

- Types A and B: Deficient acid sphingomyelinase activity results in sphingomyelin accumulation
  - Acid sphingomyelinase found in lysosomes functions in membrane degradation and turnover
  - Sphingomyelin substrate and other lipids accumulate in histiocytes
  - Over 100 mutations described in the *SMPD1* gene encoding acid sphingomyelinase
- Types C and D: Cholesterol metabolism defect leads to accumulation of cholesterol and sphingomyelin
  - Type D appears to be allelic variant of type C

CLINICAL ISSUES

Epidemiology

- Incidence
  - Estimated 0.5-1.0 cases in 100,000 newborns
- Ethnicity
  - Types A and B described in Ashkenazi Jews and individuals from North America, Western Europe, North Africa, and Middle East
  - Many patients with type D are Acadians from southwestern Nova Scotia

Presentation

- Hepatosplenomegaly with variable neurodegenerative course
  - Type A begins in utero and may present with hydrops fetalis in severe cases
  - Rapidly progressive neurodegeneration
- Type B may present in infancy, childhood, or adulthood
  - Pulmonary compromise occurs due to sphingomyelin deposition in lung parenchyma
  - Little or no neurodegenerative features seen in type B
- Types C and D can present at any age

- ○ Mild hepatosplenomegaly and may have infantile cholestasis
- ○ Slowly progressive but variable neurodegenerative disease

Treatment

- No specific treatment available

Prognosis

- Type A usually fatal by age 3
  - Type B leads to progressive liver disease, including cirrhosis, portal hypertension, and ascites
  - ○ Patients with type B frequently survive into adulthood
- Patients with type C or D develop progressive neurological deterioration
  - ○ In severe cases, may lead to death by age 3-5
  - ○ Type D follows slower neurodegenerative course than type C

MICROSCOPIC

Histologic Features

- Spotty accumulation of enlarged histiocytes in hepatic lobules and portal tracts
  - ○ Histiocyte inclusions
  - – Rounded and of fairly uniform size, imparting foamy appearance to cytoplasm
- ○ May lead to hepatic plate atrophy and fibrosis
- Hepatocytes may also accumulate sphingomyelin
- Foamy histiocytes also accumulate in other organs

ANCILLARY TESTS

Electron Microscopy

- Electron-opaque, concentrically laminated inclusions within histiocyte cytoplasm

DIFFERENTIAL DIAGNOSIS

Gaucher Disease

- Gaucher cells have striated, fibrillary cytoplasmic inclusions rather than concentrically laminated inclusionswithin histiocytes
- Gaucher inclusions accumulate in macrophages, not hepatocytes

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Hepatosplenomegaly and variably progressive neurodegenerative disease

Pathologic Interpretation Pearls

- Foamy, vacuolated histiocytes accumulate in liver and other organs

SELECTED REFERENCES

1. Schuchman, EH, et al. Types A and B Niemann-Pick disease. *Best Pract Res Clin Endocrinol Metab*. 2015; 29(2):237–247.
2. McKay Bounford, K, et al. Genetic and laboratory diagnostic approach in Niemann Pick disease type C. *J Neurol*. 2014; 261(Suppl 2):S569–S575.
3. Vanier, MT. Niemann-Pick diseases. *Handb Clin Neurol*. 2013; 113:1717–1721.
4. Schuchman, EH. The pathogenesis and treatment of acid sphingomyelinase-deficient Niemann-Pick disease. *J Inherit Metab Dis*. 2007; 30(5):654–663.

Gaucher Disease

KEY FACTS

Terminology

- Inherited deficiency of lysosomal enzyme glucocerebroside

Etiology/Pathogenesis

- Autosomal recessive trait with mutation in acid β-glucosidase gene, *GBA*
- Glucocerebroside accumulates in phagocytic cells

Clinical Issues

- Primarily involves liver, spleen, bone marrow, and bone
  - Results in hepatosplenomegaly and pancytopenia
- Variable disease progression
- Enzyme replacement therapy represents mainstay therapy
  - Early diagnosis is crucial to improving outcome

Microscopic

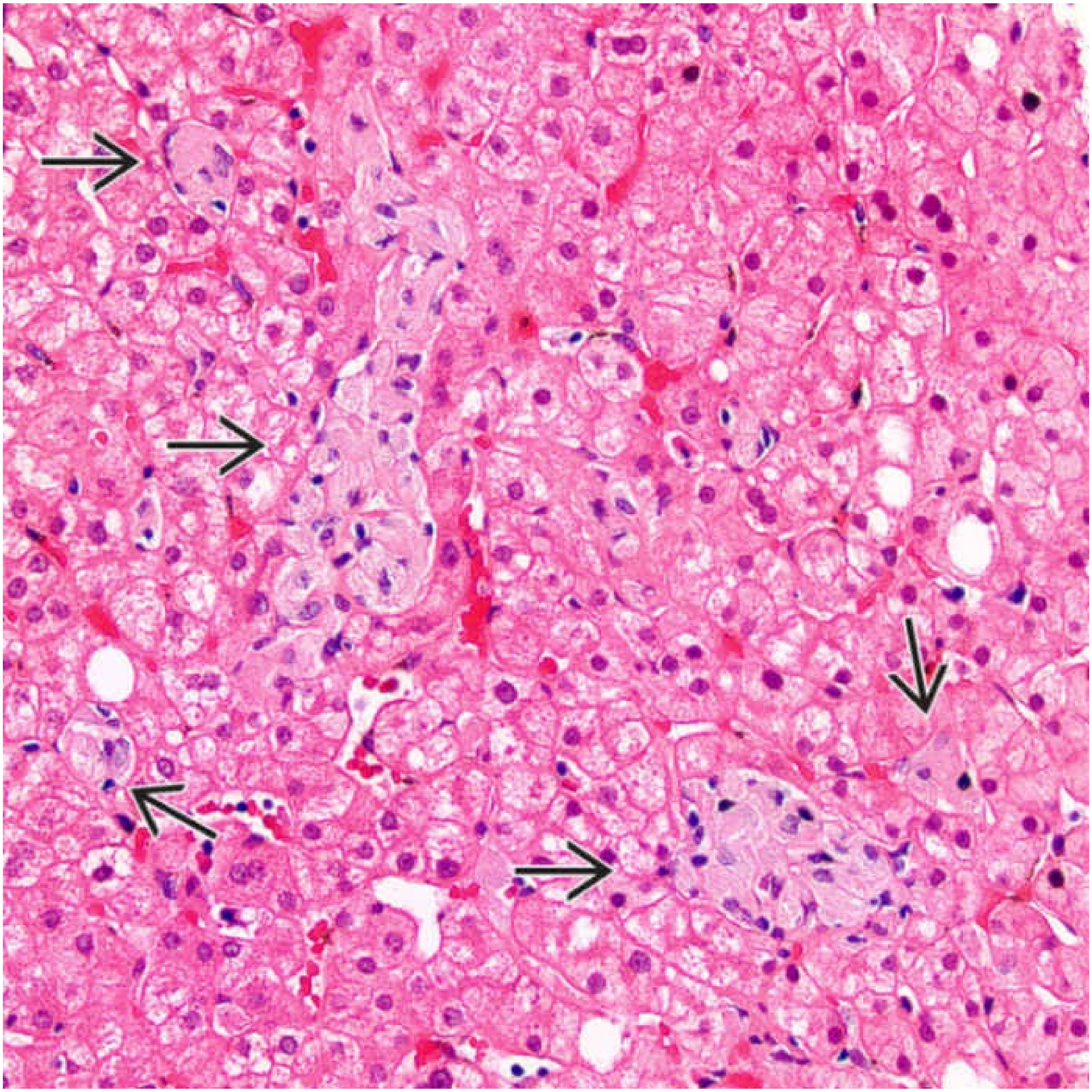
- Accumulation of glucocerebroside in Kupffer cells and portal tract macrophages results in uniquely linear amphophilic cytoplasm
  - Affected cells show characteristic linear, tissue paper-like, fibrillary, or corrugated amphophilic cytoplasm
  - Cells are positive for PAS-D
- Hepatocytes and other hepatic structures are spared

Ancillary Tests

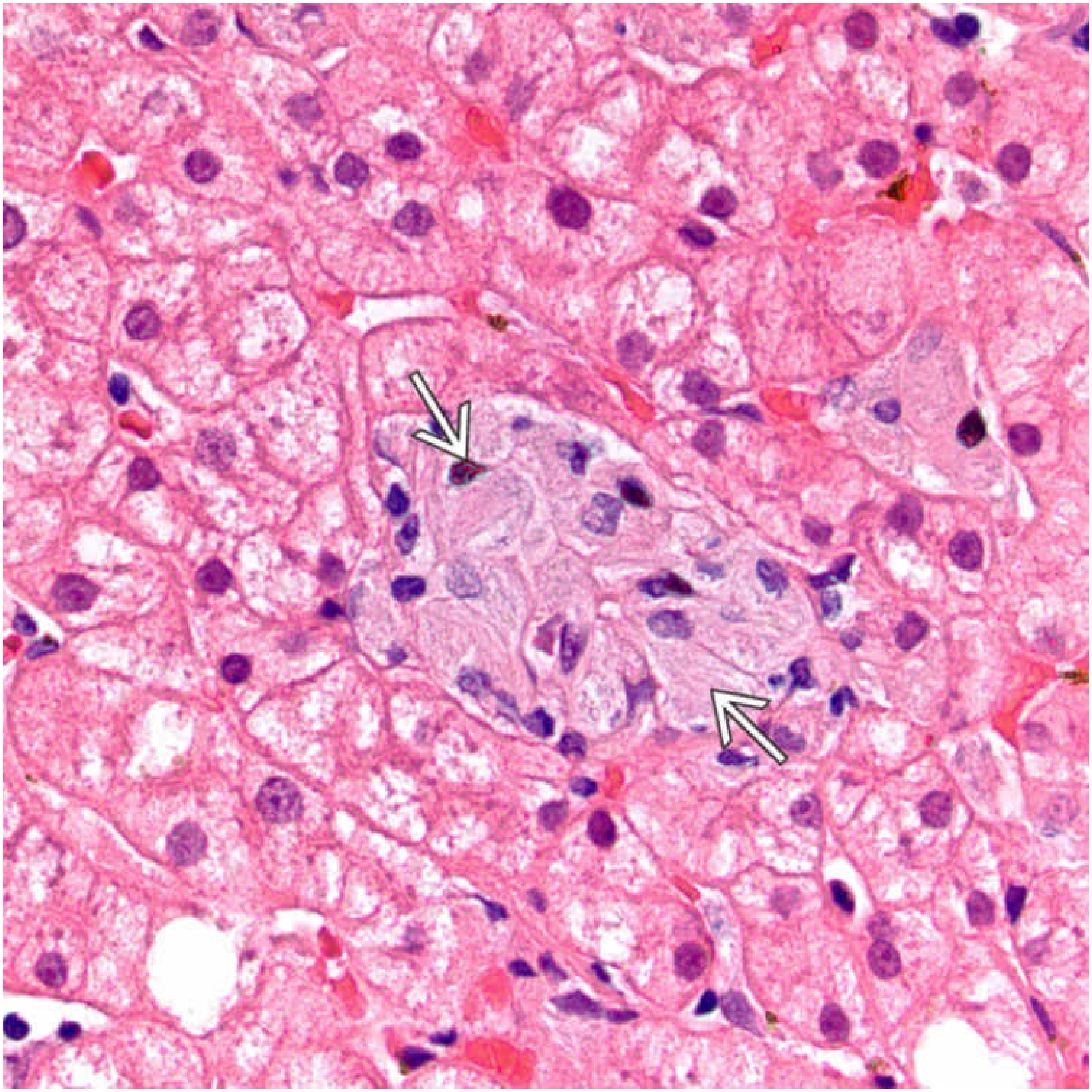
- Electron microscopy demonstrates intralysosomal compact long tubular structures

Top Differential Diagnoses

- Niemann-Pick disease
    - Enlarged Kupffer cells but foamy cytoplasm with small round vacuoles
- Wolman disease
    - Frozen section-stained slide stained with oil red O reveals abundant lipid, and polarized light highlights needle-shaped cholesterol crystals
- Pseudo-Gaucher cells in bone marrow biopsy

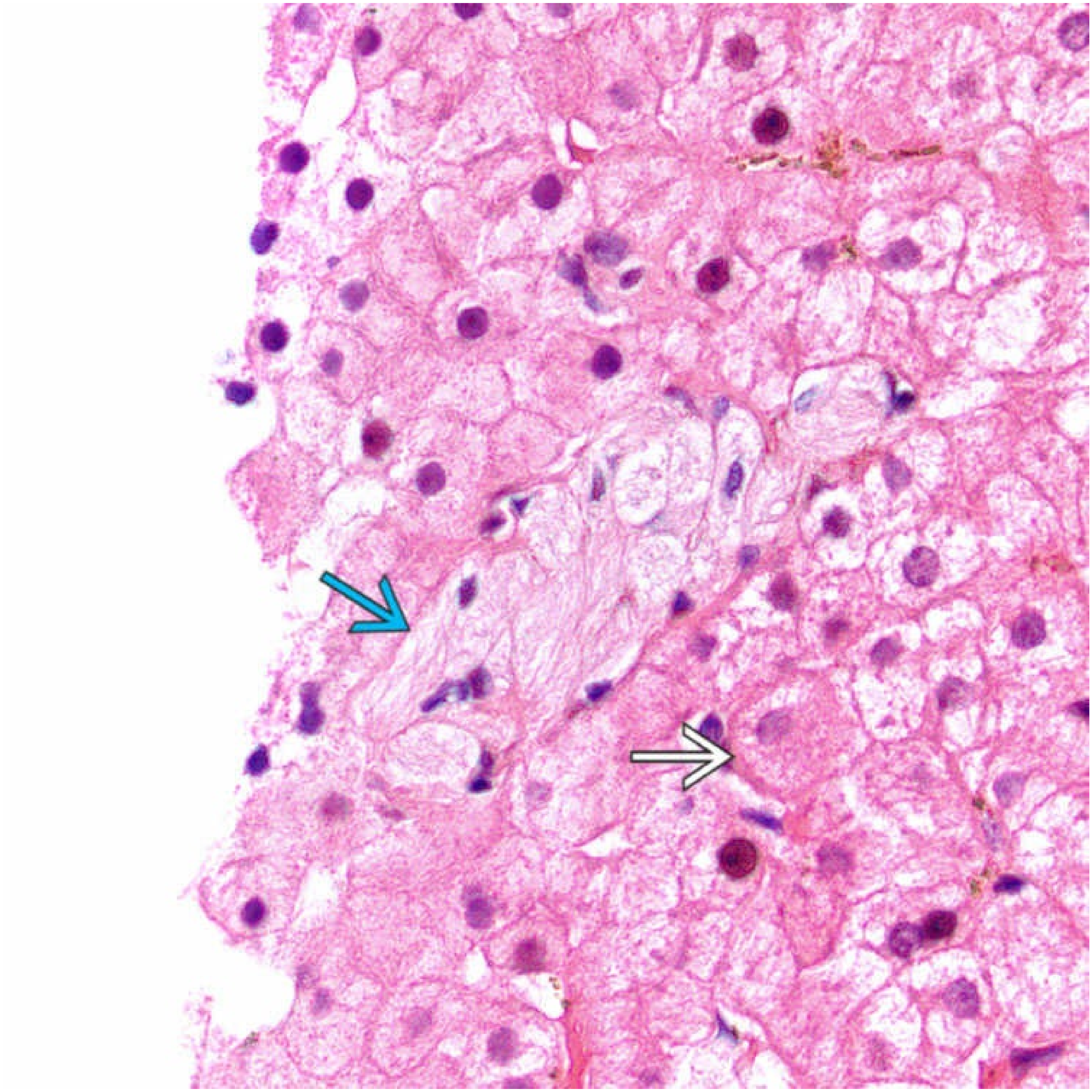


Kupffer Cell Clusters in Hepatic Lobule
Clusters of enlarged foamy Kupffer cells → with fibrillary, amphophilic cytoplasm are seen in the hepatic lobules. The clusters vary in size and shape.

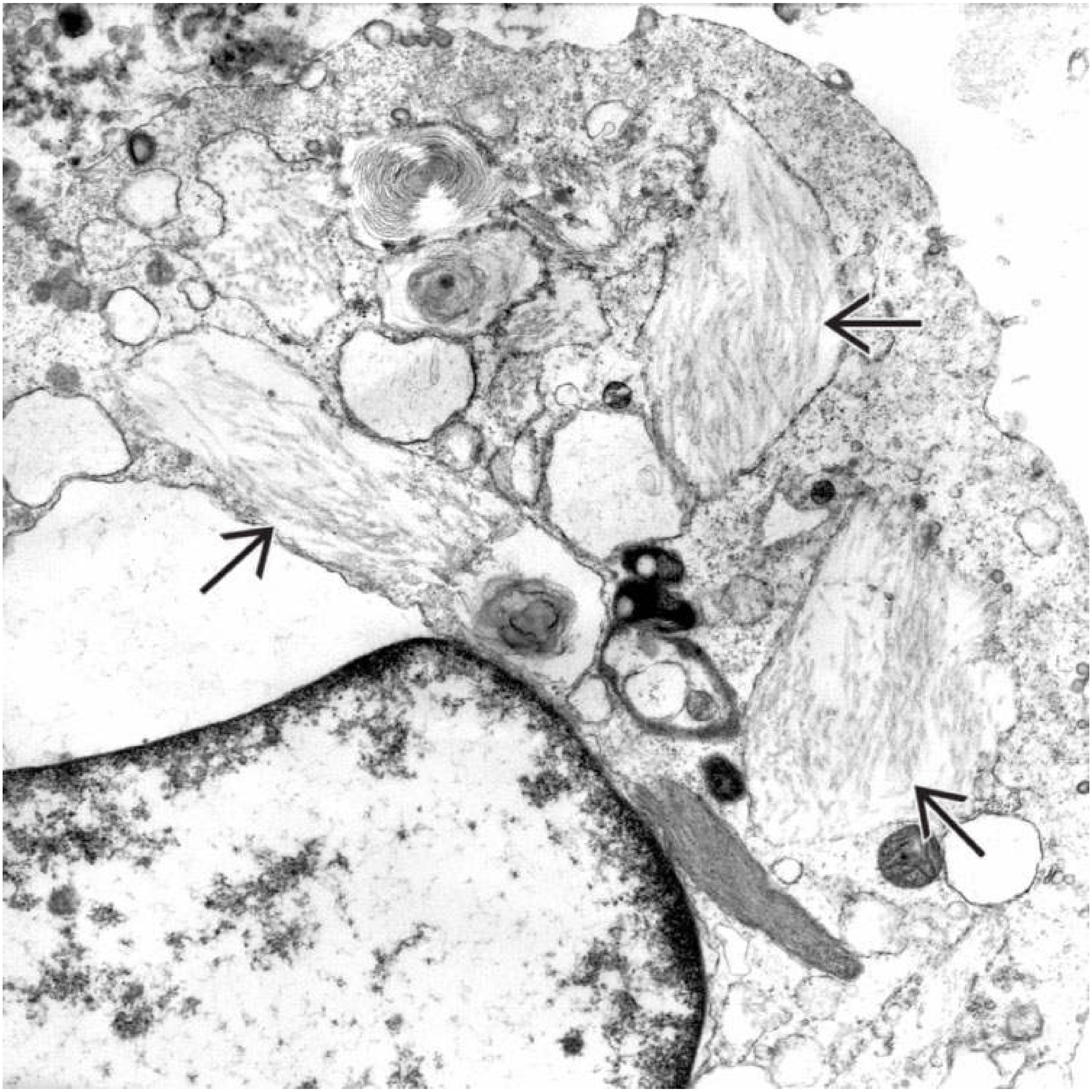


Gaucher Cells With Linear Cytoplasmic Striations

These Gaucher cells demonstrate the characteristic fibrillary or striated cytoplasm reminiscent of wrinkled tissue paper ⇒ .



Gaucher Cells Compared to Hepatocytes
In Gaucher disease, the characteristic Kupffer cell glucocerebroside inclusions exhibit a fibrillary or striated appearance. These cells have small, eccentric, and often wrinkled nuclei. In contrast, hepatocytes have more eosinophilic, granular cytoplasm and rounded nuclei .



Electron Micrograph of Gaucher Cell
Electron microscopy of a Gaucher cell demonstrates lysosomes containing numerous elongated tubular structures → that are arranged in compact bundles. (Courtesy Z. Laszik, MD, PhD.)

TERMINOLOGY

Synonyms

- Glucocerebrosidase deficiency

Definitions

- Inherited deficiency of lysosomal enzyme glucocerebrosidase

ETIOLOGY/PATHOGENESIS

Inborn Error of Metabolism

- Most common lysosomal glycolipid storage disorder
  - Acid β-glucosidase (glucocerebrosidase) enzyme deficiency
  - Accumulation of glucocerebroside (also called glucosylceramide) in phagocytic cells

Autosomal Recessive Trait

- Mutation in *GBA*, encoding acid β-glucosidase, on 1q21
- Homozygotes are affected

CLINICAL ISSUES

Site

- Visceral organs such as liver, spleen, and lung
- Bone marrow and bone
- Variably present central nervous system involvement

Presentation

- Hepatosplenomegaly
  - Pancytopenia
  - Anemia
  - Thrombocytopenia
- 3 classic clinical variants
  - Type 1 (nonneuronopathic)
    - Most common form
    - 55-60% diagnosed before 20 years of age
    - 30% diagnosed before 10 years of age
  - Types 2 and 3 (neuronopathic)

Treatment

- Enzyme replacement therapy

Prognosis

- Early diagnosis is crucial to improving outcome
- Variable disease progression

MICROSCOPIC

Histologic Features

- Accumulation and storage of glucocerebroside in Kupffer cells and macrophages
  - Spares hepatocytes
- Characteristic linear, tissue paper-like, fibrillary, or corrugated amphophilic cytoplasm
  - Cells are positive for PAS-D
- Effects secondary to sinusoidal Kupffer cell involvement are rare
  - May see atrophic hepatocytes and eventual sinusoidal fibrosis
  - Micronodular cirrhosis and hepatocellular carcinoma have been reported

ANCILLARY TESTS

Electron Microscopy

- Enlarged Kupffer cells and portal tract macrophages
  - Cytoplasm expanded by enlarged, irregular, single membrane-bound lysosomes
  - Lysosomes filled with stored glucocerebroside substance
  - – Compact long tubular structures or finely reticular to flocculent material

DIFFERENTIAL DIAGNOSIS

Niemann-Pick Disease

- Enlarged Kupffer cells but foamy cytoplasm with small round vacuoles
  - Enlarged pale hepatocytes may be indistinguishable from Kupffer cells
- Distinguished by electron microscopy
  - Concentric lamellar lipid inclusions in lysosomes of hepatocytes and Kupffer cells in Niemann-Pick disease

Wolman Disease

- Histologically similar to Niemann-Pick disease
  - Frozen section-stained slide stained with oil red O reveals abundant lipid, and polarized light highlights needle-shaped cholesterol crystals
- Distinguished by electron microscopy
  - Membrane-bound lipid droplets in hepatocytes and Kupffer cells
  - Cholesterol crystals in hepatocytes and Kupffer cells

Pseudo-Gaucher Cells in Bone Marrow Biopsy

- Resulting from high rate of cell turnover
- Can be found in chronic myelogenous leukemia

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Accumulation of glucocerebroside in Kupffer cells and macrophages but not hepatocytes
- Electron microscopy demonstrates intralysosomal rod-shaped inclusions

SELECTED REFERENCES

1. Chen, M, et al. Gaucher disease: review of the literature. *Arch Pathol Lab Med*. 2008; 132(5):851–853.
2. Niederau, C, et al. Gaucher's disease: a review for the internist and hepatologist. *Hepatogastroenterology*. 2000; 47(34):984–997.
3. Pastores, GM. Gaucher's Disease. Pathological features. *Baillieres Clin Haematol*. 1997; 10(4):739–749.
4. Lee, RE. The pathology of Gaucher disease. *Prog Clin Biol Res*. 1982; 95:177–217.
5. James, SP, et al. Liver abnormalities in patients with Gaucher's disease. *Gastroenterology*. 1981; 80(1):126–133.
6. Lee, RE, et al. Gaucher's disease. I. Modern enzymatic and anatomic methods of diagnosis. *Arch Pathol Lab Med*. 1981; 105(2):102–104.
7. Lee, RE, et al. Gaucher's disease: clinical, morphologic, and pathogenetic considerations. *Pathol Annu*. 1977; 12(Pt 2):309–339.
8. Hibbs, RG, et al. A histochemical and electron microscopic study of Gaucher cells. *Arch Pathol*. 1970; 89(2):137–153.

Neonatal Hemochromatosis

KEY FACTS

Terminology

- Neonatal hemochromatosis (NH)
- Severe liver disease with iron overload in liver and other organs (distribution similar to hereditary hemochromatosis)

Clinical Issues

- Intrauterine growth retardation, oligohydramnios, stillborn or premature birth
  - Involving
    - Liver
    - Pancreas
    - Heart
    - Thyroid
    - Minor salivary glands
- Abnormal iron studies
- Liver and multiorgan failure

Macroscopic

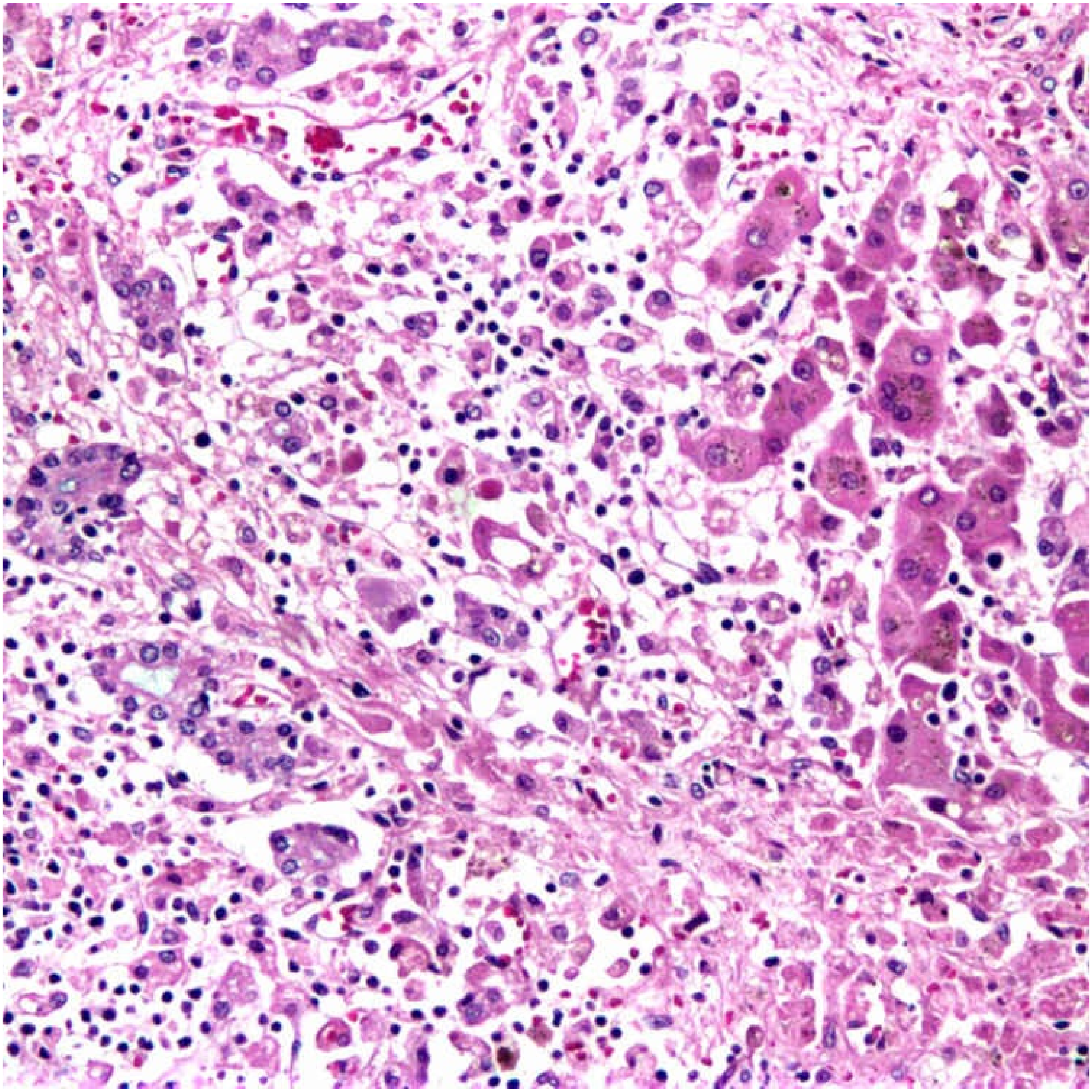
- Shrunken liver
- Cirrhosis

Microscopic

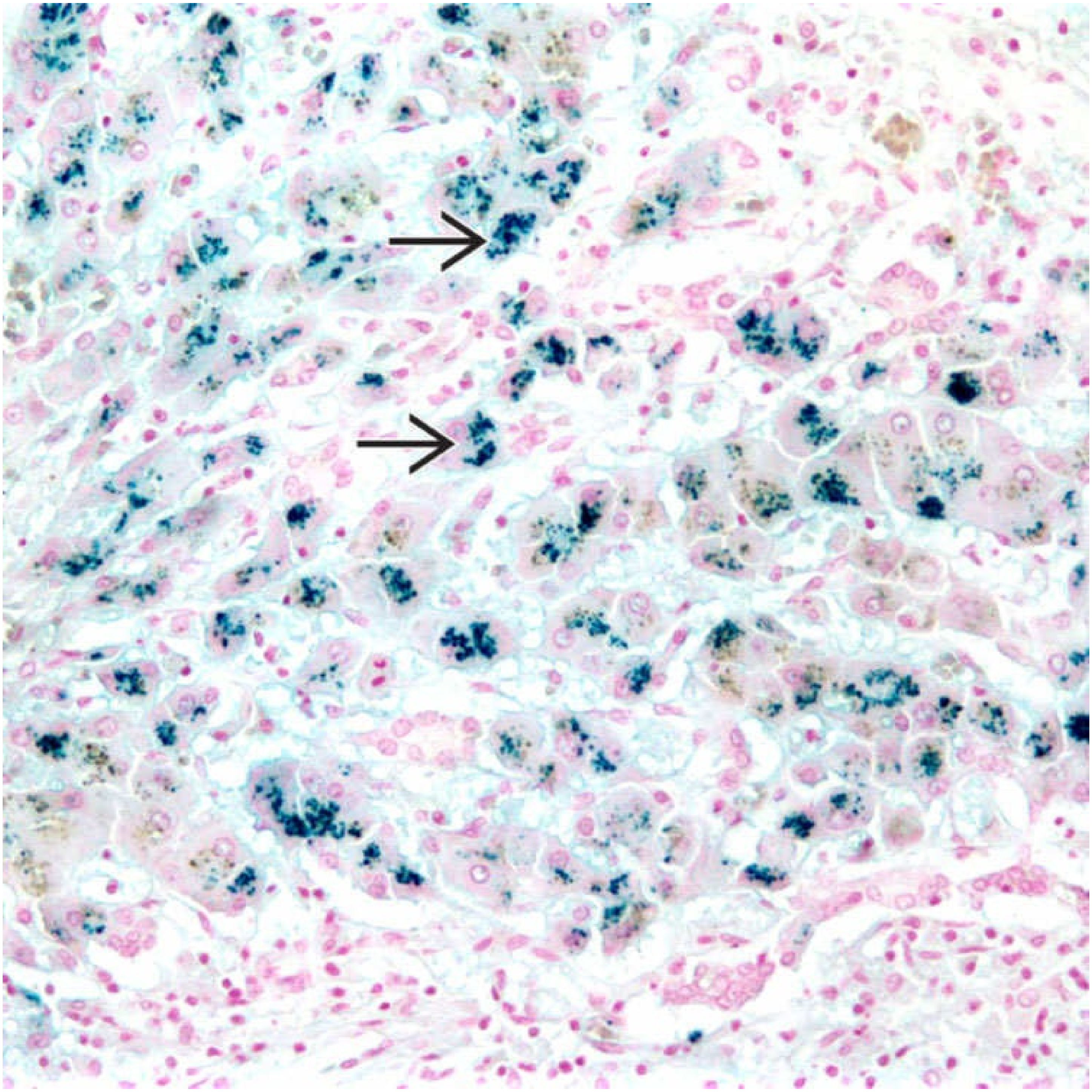
- Marked lobular necrosis with collapse
- Regenerative nodules
- Pseudoacinar formation
- Intracanalicular bile plugs
- Giant hepatocytes
- Iron deposition in hepatocytes and ductules as well as in organs outside of liver

Top Differential Diagnoses

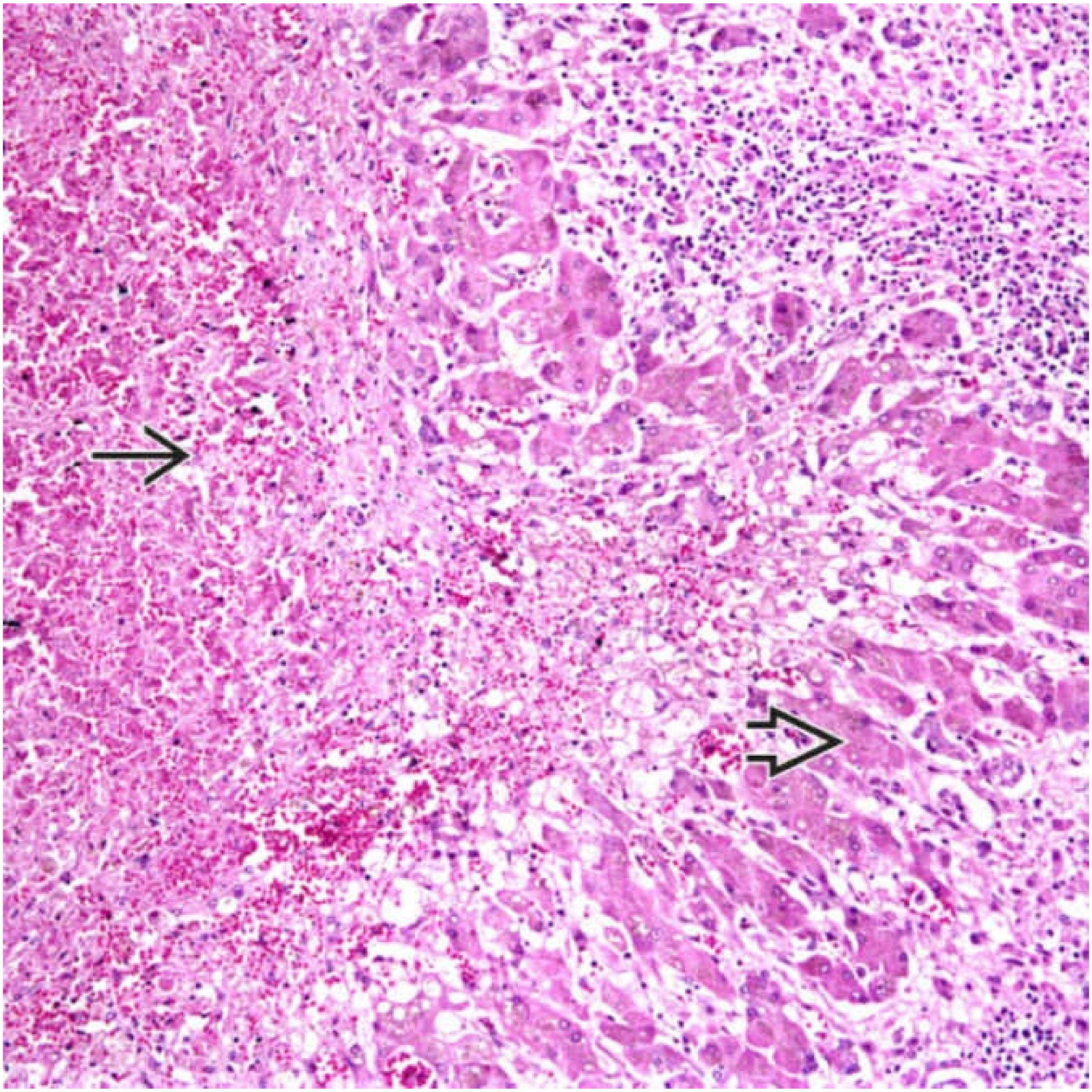
- Virus infection
  - CMV
  - Echovirus
  - Herpes simplex virus
- Neonatal lupus
- Tyrosinemia



Lobular Necrosis
H&E in this case of neonatal hemochromatosis shows lobular necrosis and collapse of the hepatocellular cords with residual hepatocytes and bile ductules.

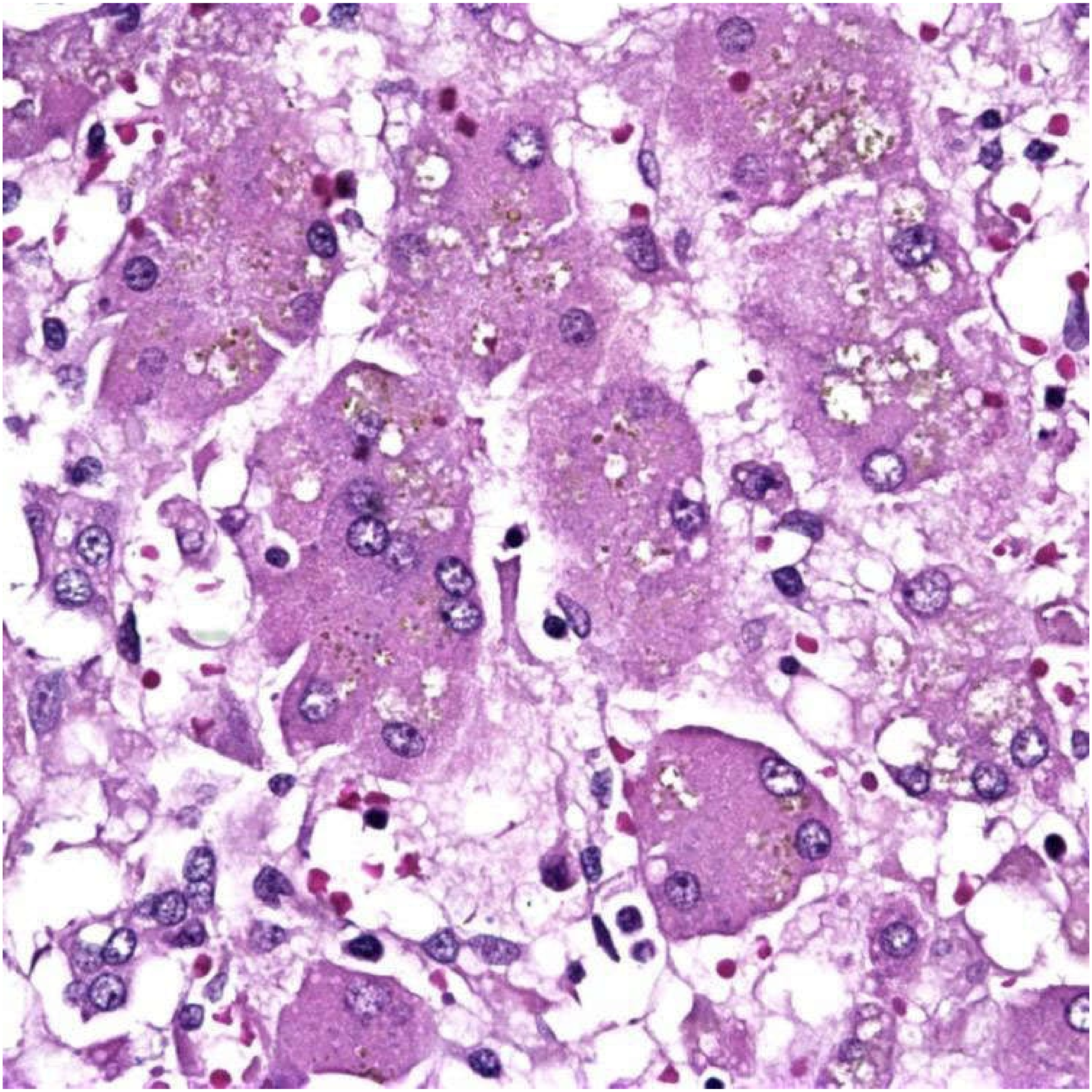


Perl Iron Stain
Perl iron stain in this case of neonatal hemochromatosis shows marked iron deposition → within the hepatocytes.



Submassive Hepatocellular Necrosis

Higher power of this case of neonatal hemochromatosis shows submassive hepatocellular necrosis → with a rim of residual hepatocytes ⇨ .



Giant Cells
Giant cells are seen in this case of neonatal hemochromatosis.

TERMINOLOGY

Abbreviations

- Neonatal hemochromatosis (NH)

Synonyms

- Congenital hemochromatosis
- Neonatal iron storage disease

- Gestational alloimmune disease

Definitions

- Severe liver disease with iron overload in liver and other organs (distribution similar to hereditary hemochromatosis)
  - Fetal or perinatal onset
  - Without hereditary hemochromatosis gene mutation

ETIOLOGY/PATHOGENESIS

Unknown

- Etiology remains unclear though alloimmune liver injury has been suggested

CLINICAL ISSUES

Epidemiology

- Incidence
  - Extremely rare

Site

- Liver, pancreas, heart, thyroid, minor salivary glands

Presentation

- Intrauterine growth retardation
  - Oligohydramnios
  - Stillborn or premature birth
  - Severe fetal liver failure
  - Jaundice with elevated bilirubin
  - Coagulopathy
  - Hypoalbuminemia, edema, ascites
  - Very high α-fetoprotein (AFP)
  - – Disproportionately low aminotransferases
- Multiorgan failure
  - Sepsis
  - Hypoglycemia
  - Oliguria
- Abnormal iron studies
  - Hypotransferrinemia
  - Hyperferritinemia

Laboratory Tests

- Elevated hepatic iron concentration
  - 240 to 38,200 μg/g dry weight (healthy neonate 250 μg/g dry weight)

Treatment

- Drug cocktail containing antioxidants and iron chelator
- Supportive care
- Liver transplantation

Prognosis

- Generally very poor

IMAGING

MR Findings

- Iron deposition may be found on
  - Liver
  - Pancreas
  - Heart

MACROSCOPIC

General Features

- Cirrhosis, shrunken liver

MICROSCOPIC

Histologic Features

- Marked lobular necrosis
  - Accompanied by parenchymal collapse
- Regenerative nodule formation
- Giant cell transformation of hepatocytes
- Pseudoacinar formation
- Intracanalicular bile plugs
- Iron-laden hepatocytes and ductules
  - Highlighted by iron stain
  - Sparing of reticuloendothelial system
- Also features abnormal iron deposition in other organs

Predominant Pattern/Injury Type

- Abnormal accumulation

Predominant Cell/Compartment Type

- Hepatocytes

Lip Biopsy

- Diagnostic adjunct
  - Hemosiderin accumulates in acinar epithelial cells of labial minor salivary gland

DIFFERENTIAL DIAGNOSIS

Viral Infection

- Look for inclusions, evidence of virus on EM

Neonatal Lupus

- Infants have ANA(+), lupoid antibodies on immunofluorescence

Tyrosinemia

- Urinary excretion of toxic metabolites

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Abnormal hepatic iron accumulation in severely ill neonate

Pathologic Interpretation Pearls

- Abnormal iron accumulation in tissues

SELECTED REFERENCES

1. Chan, KC, et al. Labial salivary gland involvement in neonatal hemochromatosis: a report of 2 cases and review of literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2008; 106(1):e27–e30.
2. Whitington, PF. Fetal and infantile hemochromatosis. *Hepatology*. 2006; 43(4):654–660.

3. Knisely, AS, et al. Neonatal hemochromatosis. *Gastroenterol Clin North Am*. 2003; 32(3):877–889. [vi-vii].
4. Murray, KF, et al. Neonatal hemochromatosis. *Pediatrics*. 2001; 108(4):960–964.
5. Kershisnik, MM, et al. Cytomegalovirus infection, fetal liver disease, and neonatal hemochromatosis. *Hum Pathol*. 1992; 23(9):1075–1080.

Porphyrin Metabolism Disorders

KEY FACTS

Terminology

- Heterogeneous group of inherited and acquired disorders of heme biosynthesis
  - Porphyria cutanea tarda (PCT) and erythropoietic protoporphyria (EP) associated with hepatic pathology
- Terms “hepatic” or “erythropoietic” porphyria based on site of heme precursor accumulation

Etiology/Pathogenesis

- Genetic: Defect in 1 of 8 enzymes involved in heme synthesis
  - EP due to partial deficiency of ferrochelatase activity
  - Familial PCT due to deficiency of uroporphyrinogen decarboxylase activity in all tissues
- Sporadic PCT is primarily an acquired disorder
  - Precipitating factors include hepatitis C virus (HCV), *HFE* mutations, alcohol, and drugs

Clinical Issues

- Photosensitivity, variable liver disease

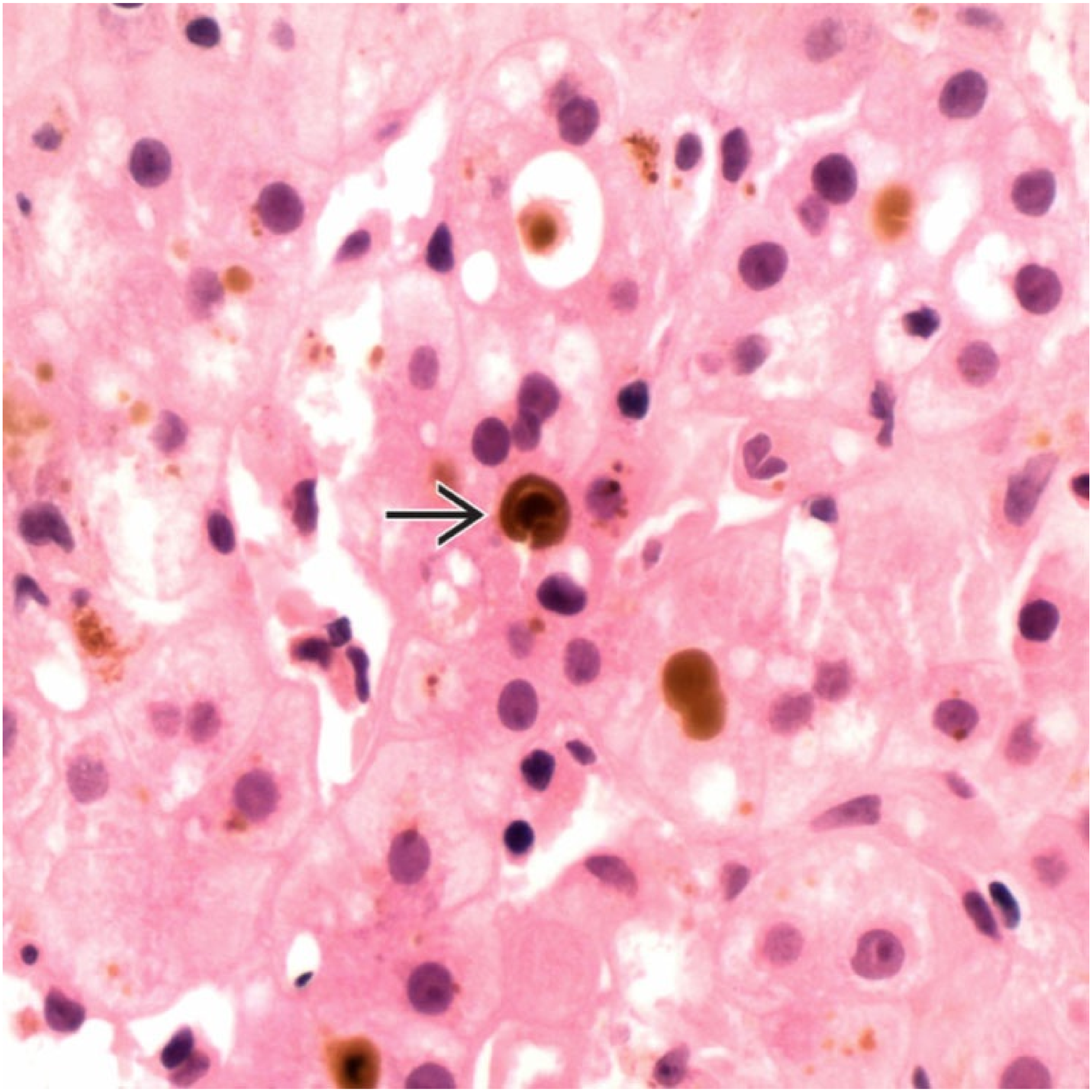
Microscopic

- PCT: Mild to moderate siderosis, steatosis, changes typical of HCV
- EP: Cholestasis; red-brown aggregates of protoporphyrin in canaliculi, hepatocytes, Kupffer cells

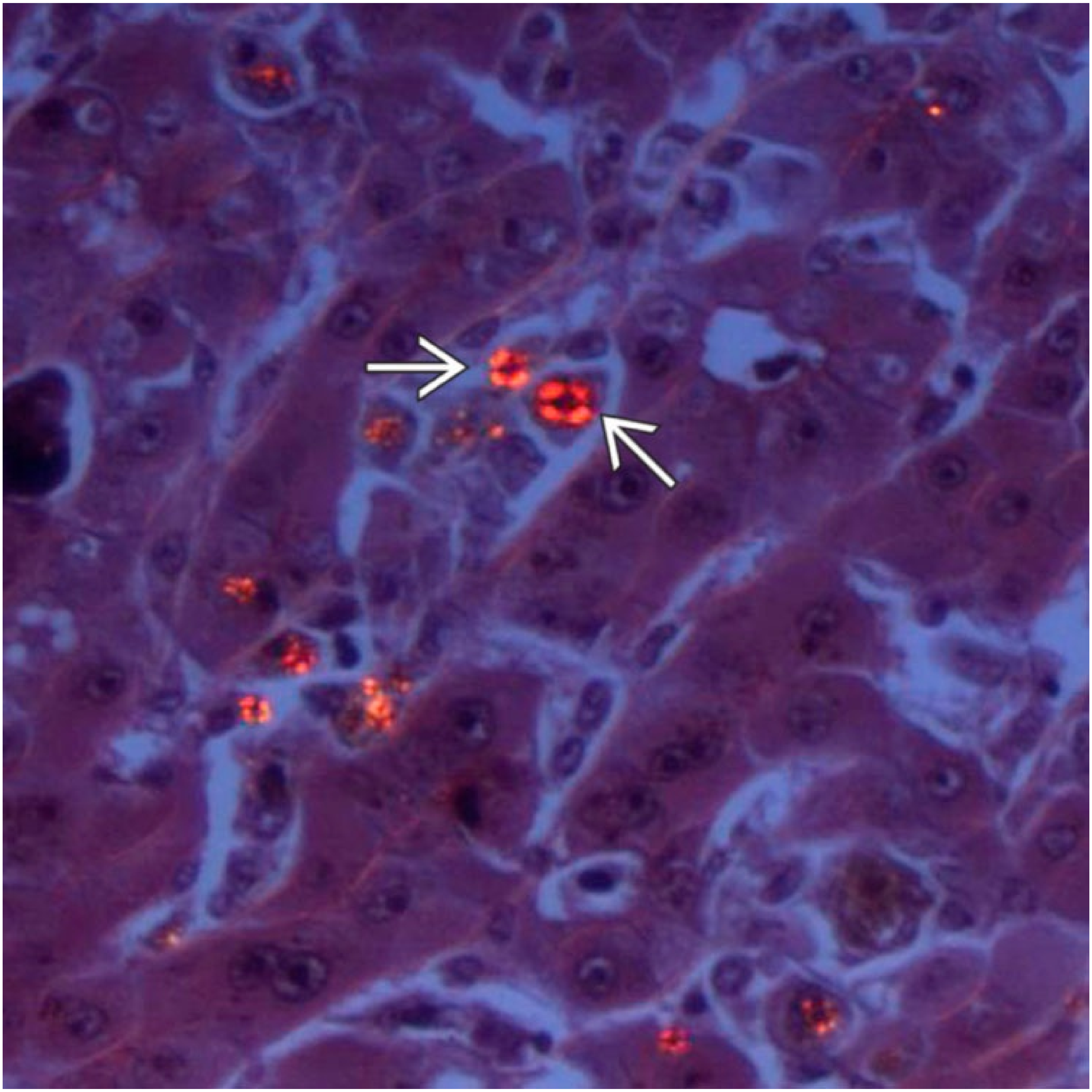
Ancillary Tests

- PCT
  - Electron microscopy
  - Polarization microscopy
  - Ferric ferricyanide stain
  - Laboratory testing for porphyrins

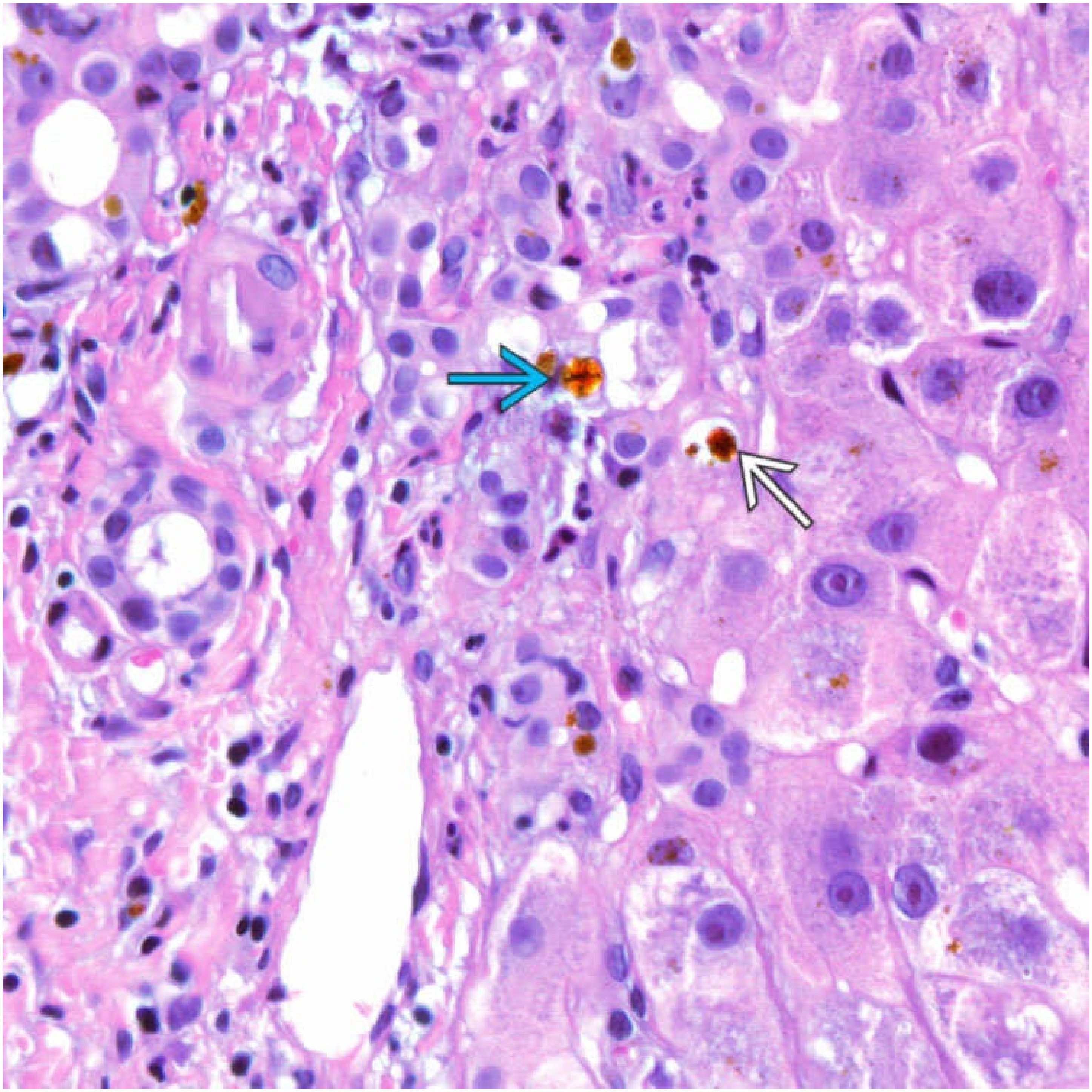
- EP
  - Electron microscopy
  - Polarization microscopy
  - Laboratory testing for porphyrins



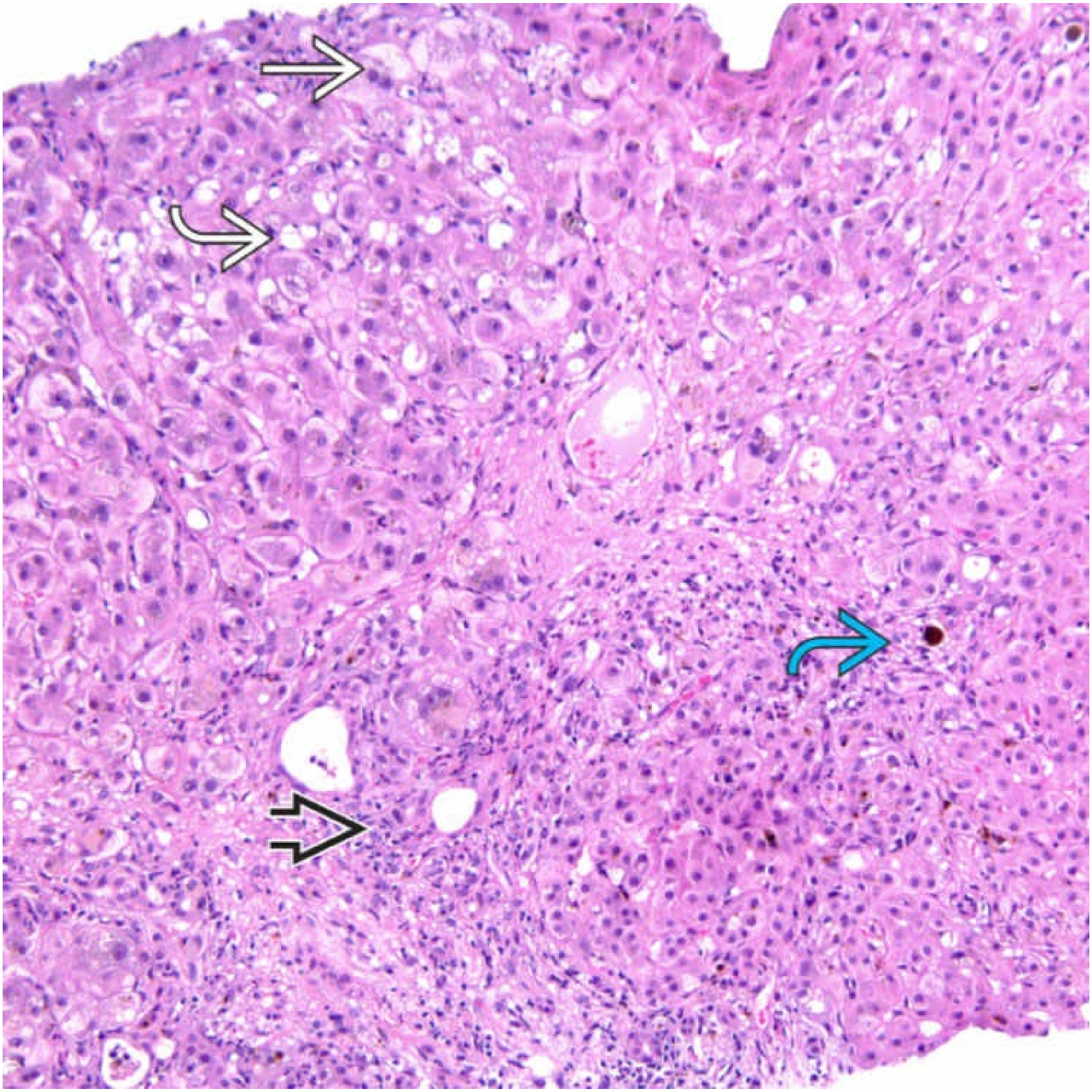
Cholestasis and Deposits in EP
Erythropoietic protoporphyria (EP) features cholestasis and rust-brown deposits → in both hepatocytes and canaliculi.



Maltese Crosses of EP Under Polarized Light
When viewed under polarized light, EP shows birefringent protoporphyrin deposits that are brightly birefringent and have a Maltese cross appearance .



Maltese Crosses of EP Under Polarized Light
When viewed under polarized light, protoporphyrin deposits exhibit the characteristic Maltese cross configuration →. Additional red-brown protoporphyrin deposits ⇒ are also visible.



Low-Power View
H&E-stained slide shows a background of mild steatosis, mild portal inflammation, and hepatocyte swelling in a patient with EP. The red-brown protoporphyrin deposits are also visible.

TERMINOLOGY

Abbreviations

- Porphyria cutanea tarda (PCT)
- Erythropoietic protoporphyria (EP)

Synonyms

• EP also termed erythrohepatic protoporphyria and protoporphyria

Definitions

• Heterogeneous set of disorders of heme biosynthesis, resulting in accumulation of heme precursors
  ○ PCT and EP are associated with hepatic pathology
• Terms “hepatic” or “erythropoietic” porphyria based on site of heme precursor accumulation

ETIOLOGY/PATHOGENESIS

Genetic Disorder: EP and Type II (Familial) PCT

• Defect in 1 of 8 enzymes involved in heme synthesis
  • EP: Partial deficiency of ferrochelatase activity
  • Type II (familial) PCT: 20% of PCT patients
  ○ Heterozygous uroporphyrinogen decarboxylase (*UROD*) mutation

Type I (Sporadic) PCT: Acquired Disorder

• 80% of PCT patients lack genetic defect but have acquired UROD deficiency in liver only
  • Associated with various other genetic and acquired conditions
  ○ Conditions that increase iron absorption (e.g., *HFE* mutations)
  ○ Hepatitis C virus (HCV) infection
  ○ Alcohol, HIV, estrogen use, smoking, low vitamin C, and carotenoid status

Type III PCT: Cause Unknown

• < 5% of PCT patients have positive family history but no known underlying genetic defect

CLINICAL ISSUES

Epidemiology

• Incidence
  ○ PCT: 1 in 25,000 persons in North America but higher in some European countries and South African Bantu population
  ○ EP: 1 in 75,000-200,000 persons among some Western European populations
• Age
  ○ Sporadic PCT occurs in patients 40-50 years of age
  ○ Familial PCT occurs early, sometimes in childhood
  ○ EP presents with photosensitivity in childhood, but liver disease usually presents after age 30
• Sex
  ○ Sporadic PCT and EP occur more often in male patients

Presentation

- PCT: Blistering skin condition on sun-exposed areas and abnormal liver function tests
  - EP: Transient cutaneous erythema and swelling immediately after sun exposure
  - Minority of patients develop severe liver disease

Laboratory Tests

- Porphyrins in urine, feces, and, in some cases, erythrocytes

Treatment

- PCT: Phlebotomy, low-dose chloroquine; avoid sun exposure, alcohol, and estrogens
- EP: β-carotene, cholestyramine; avoid sun exposure

Prognosis

- PCT: Good prognosis, although increased risk of cirrhosis and hepatocellular carcinoma (especially with HCV)
  - EP: Prognosis varies with presence and degree of liver damage
  - Liver transplantation improves survival but not curative since excess porphyrin is produced in bone marrow (not liver)

MACROSCOPIC

General Features

- EP: Black appearance to liver

MICROSCOPIC

Histologic Features

- PCT
  - Needle-shaped cytoplasmic hepatocyte inclusions difficult to identify on H&E; rarely seen on unstained sections by light microscopy or polarizing light or ferric ferricyanide stain
  - Steatosis, variable siderosis, and fibrosis
  - Features of concomitant HCV infection if HCV positive
- EP
  - Cholestasis
  - Red-brown protoporphyrin deposits in canaliculi, hepatocytes, and Kupffer cells
    - Birefringent on polarizing microscopy
    - Some show Maltese cross configuration
  - Variable fibrosis or cirrhosis

ANCILLARY TESTS

Electron Microscopy

- PCT shows needle-like structures in hepatocytes
- EP shows aggregates of radiating crystals in dilated canaliculi, hepatocyte vacuoles, and Kupffer cells

DIFFERENTIAL DIAGNOSIS

Hepatitis C Infection

- No needle-like structures in hepatocytes; no skin blistering

Hemochromatosis

- Not associated with skin blistering

Cholestasis

- Inspissated material of EP is more red-brown; polarization microscopy shows birefringence and Maltese cross configuration in deposits

DIAGNOSTIC CHECKLIST

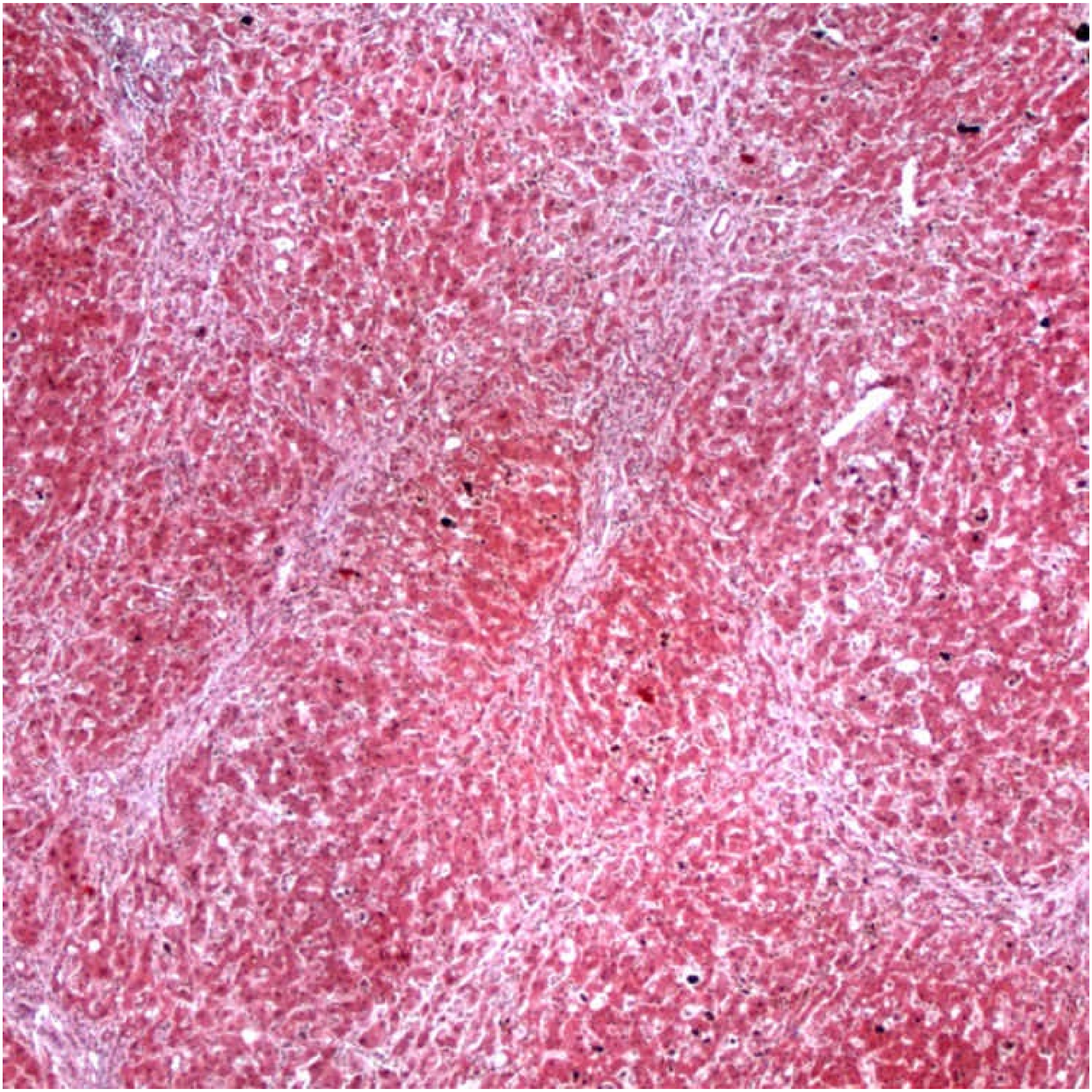
Clinically Relevant Pathologic Features

- Patients have photosensitivity, variable degree of liver disease

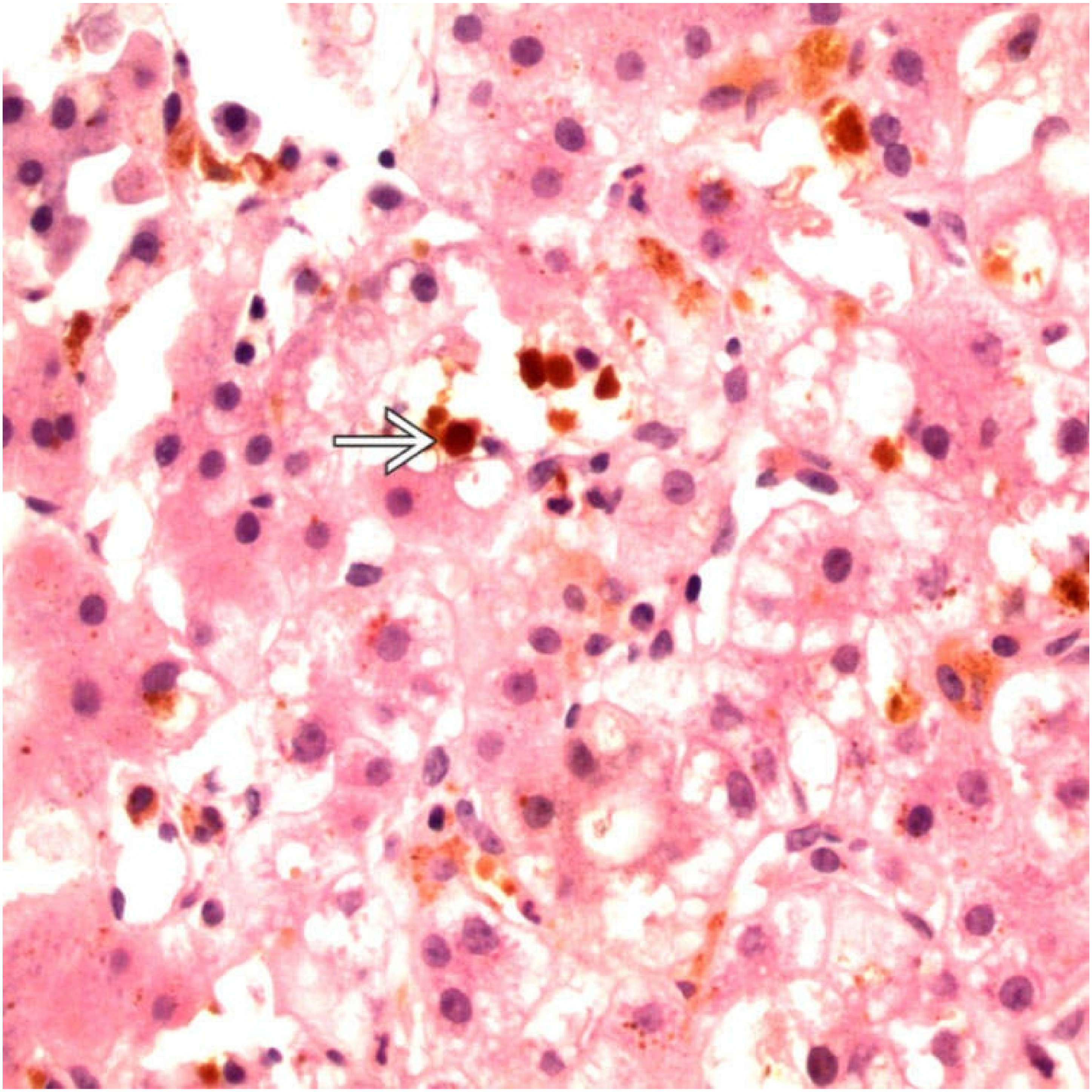
Pathologic Interpretation Pearls

- PCT: Nonspecific siderosis, features of HCV; inclusions difficult to identify on H&E
- EP: Look for red-brown inclusions in hepatocytes

Black Liver in EP
This gross specimen of a liver in EP shows the typical black discoloration.

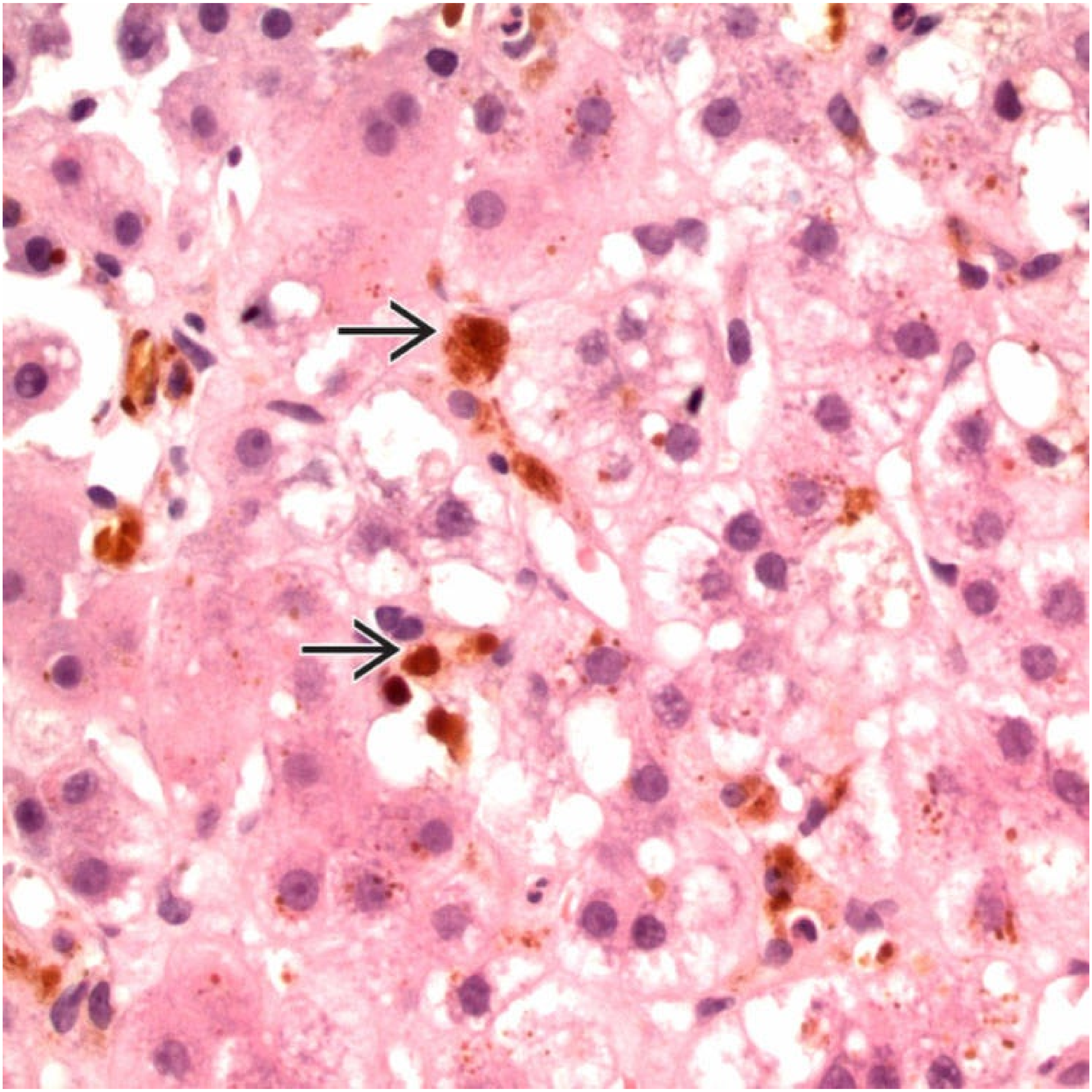


Bridging Fibrosis in EP
Trichrome stain shows increased fibrosis with bridging in EP.

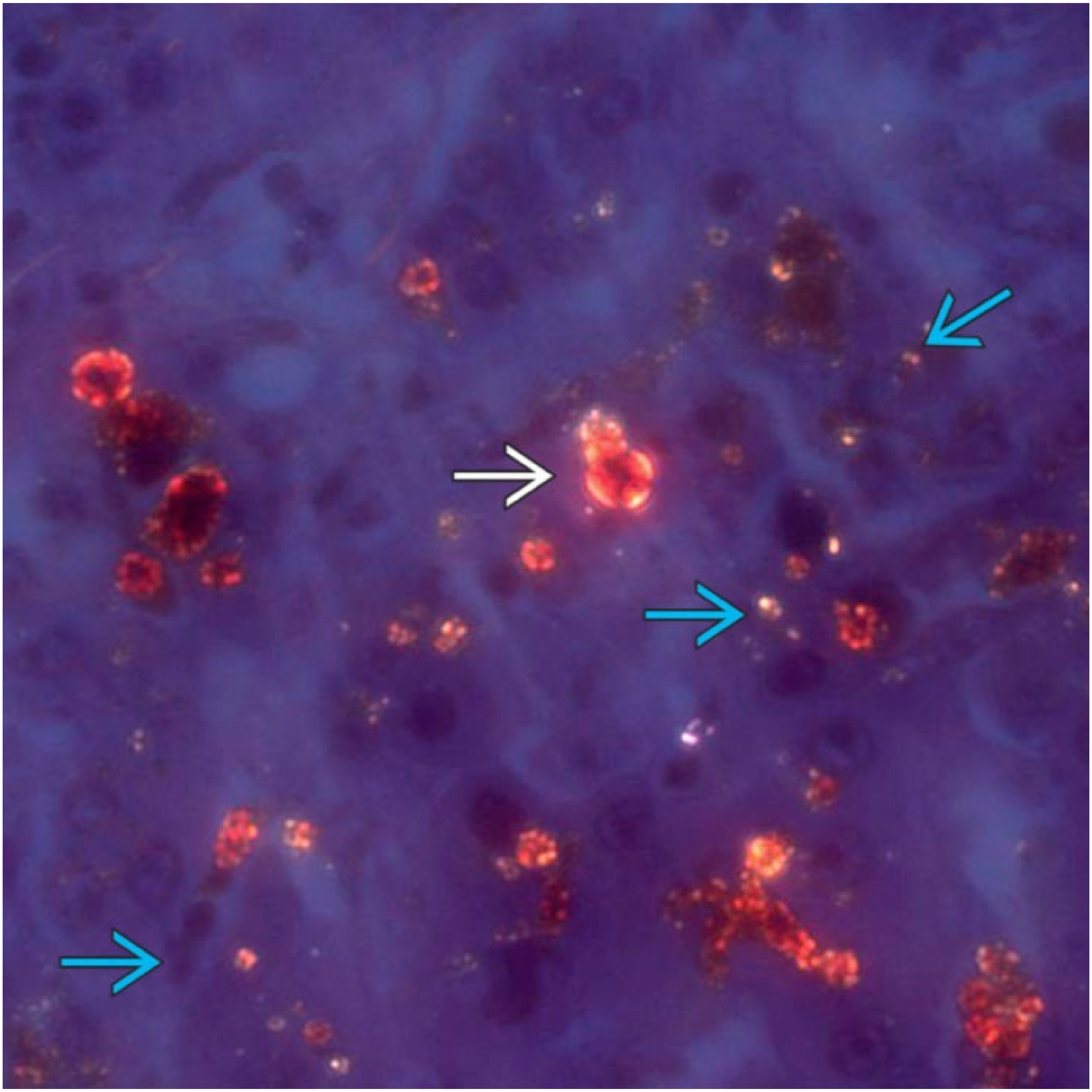


Protoporphyrin Deposits in EP

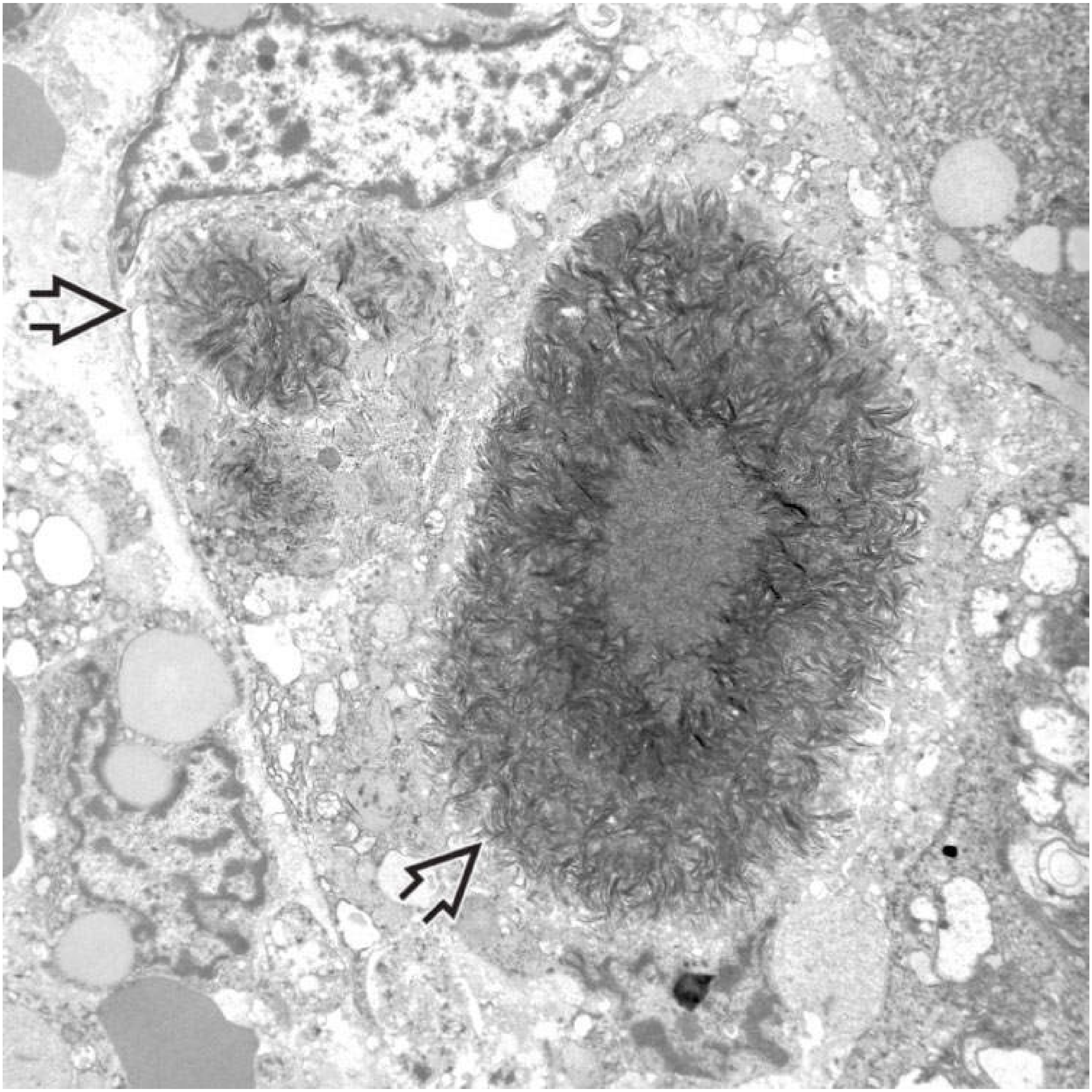
EP shows cholestasis and brown deposits of protoporphyrin ⇒ in the liver parenchyma with associated degenerative changes in hepatocytes.



Protoporphyrin and Hepatocyte Swelling in EP
EP shows cholestasis and brown protoporphyrin deposits → in a background of vacuolated and mildly swollen hepatocytes.

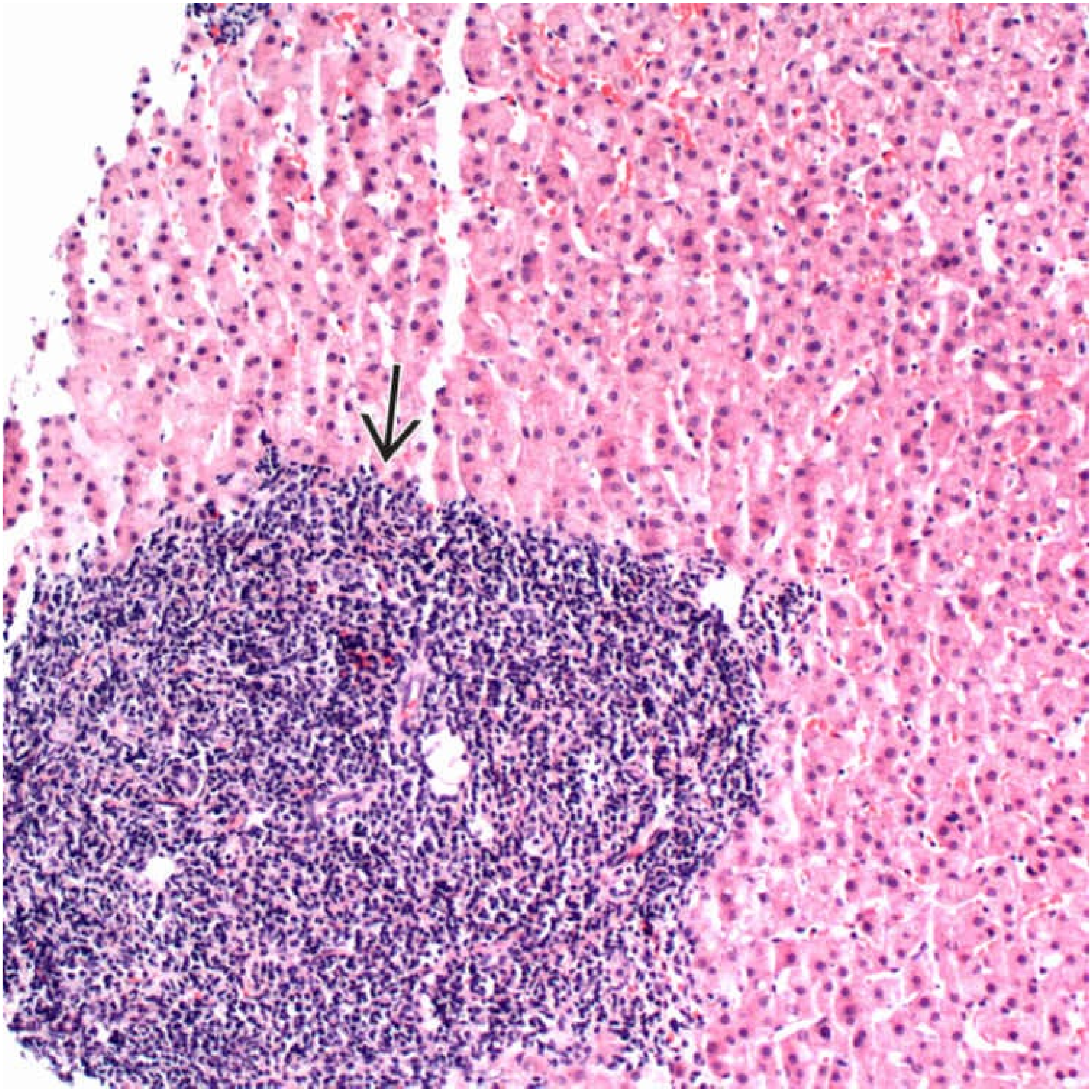


EP Under Polarized Light
H&E section under polarized light shows a large protoporphyrin deposit with the Maltese cross configuration, whereas other deposits confer a starry-sky appearance.



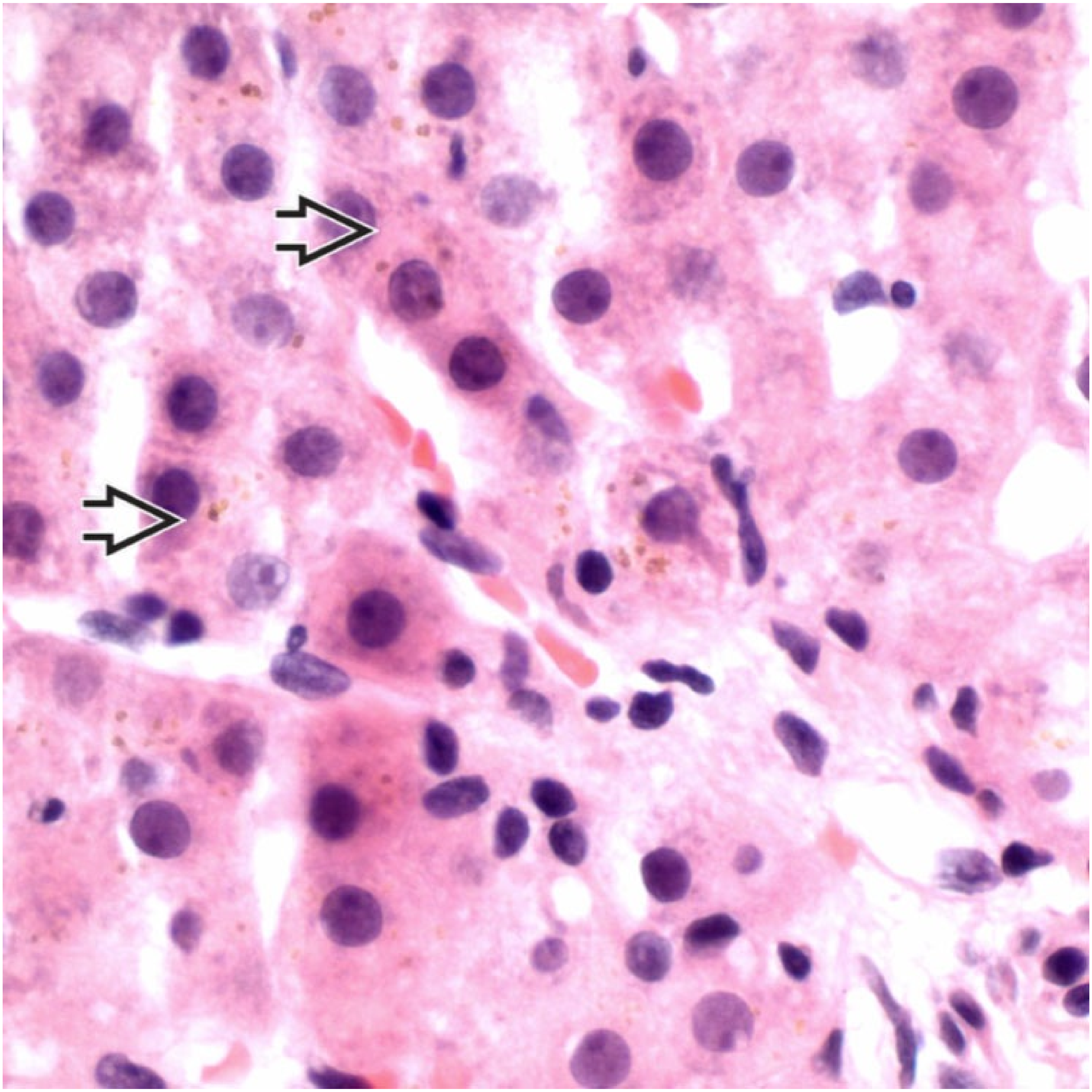
Electron Microscopy of Protoporphyrin Crystals

Electron micrograph shows aggregates of crystals of protoporphyrin in a radiating pattern ➩ in EP.



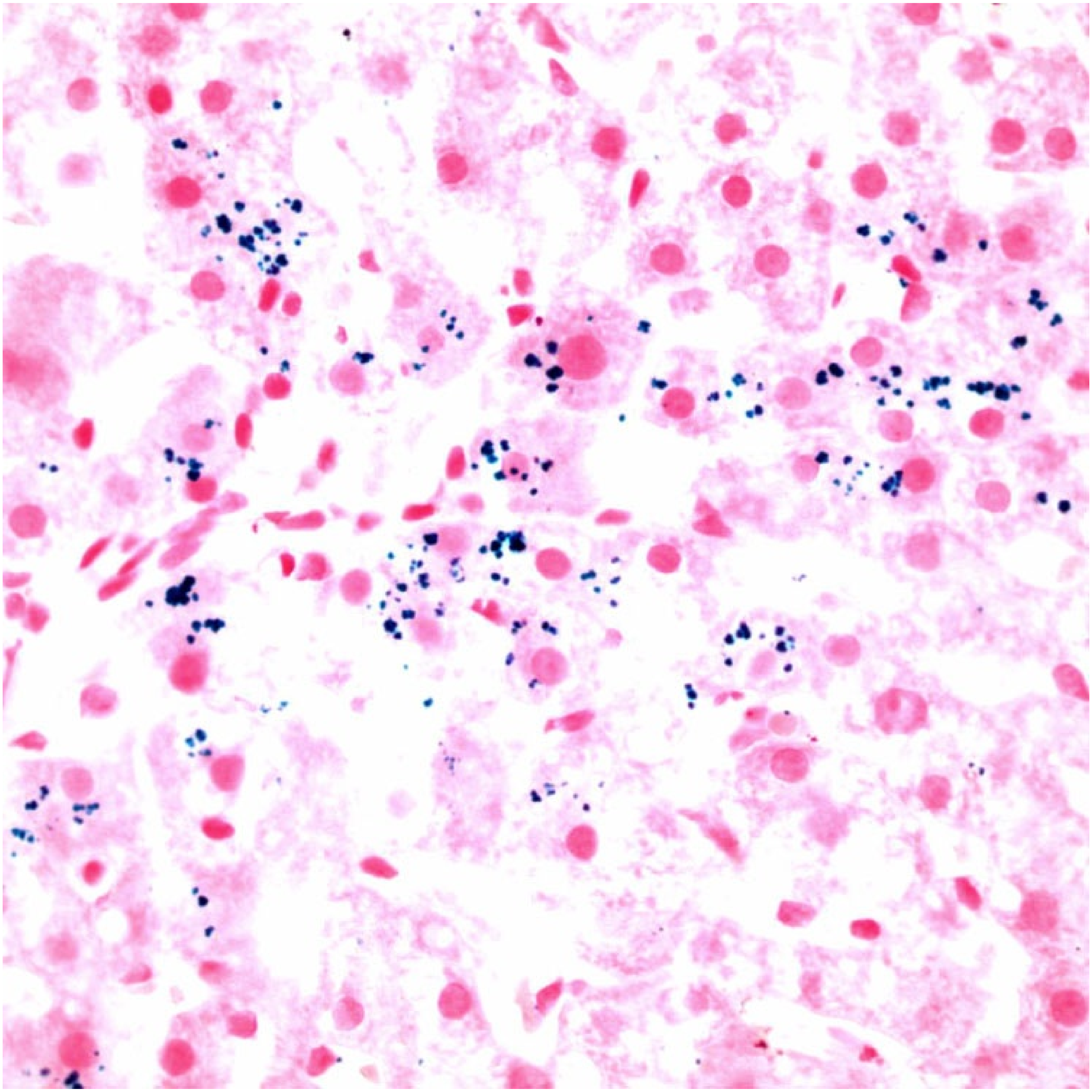
Chronic Hepatitis in Patient With HCV and PCT

A dense portal lymphoid aggregate →, characteristic of hepatitis C virus (HCV) infection, is seen in this patient with HCV and porphyria cutanea tarda (PCT). More than 1/2 of patients with sporadic PCT also have HCV with biopsy findings typical of HCV infection.



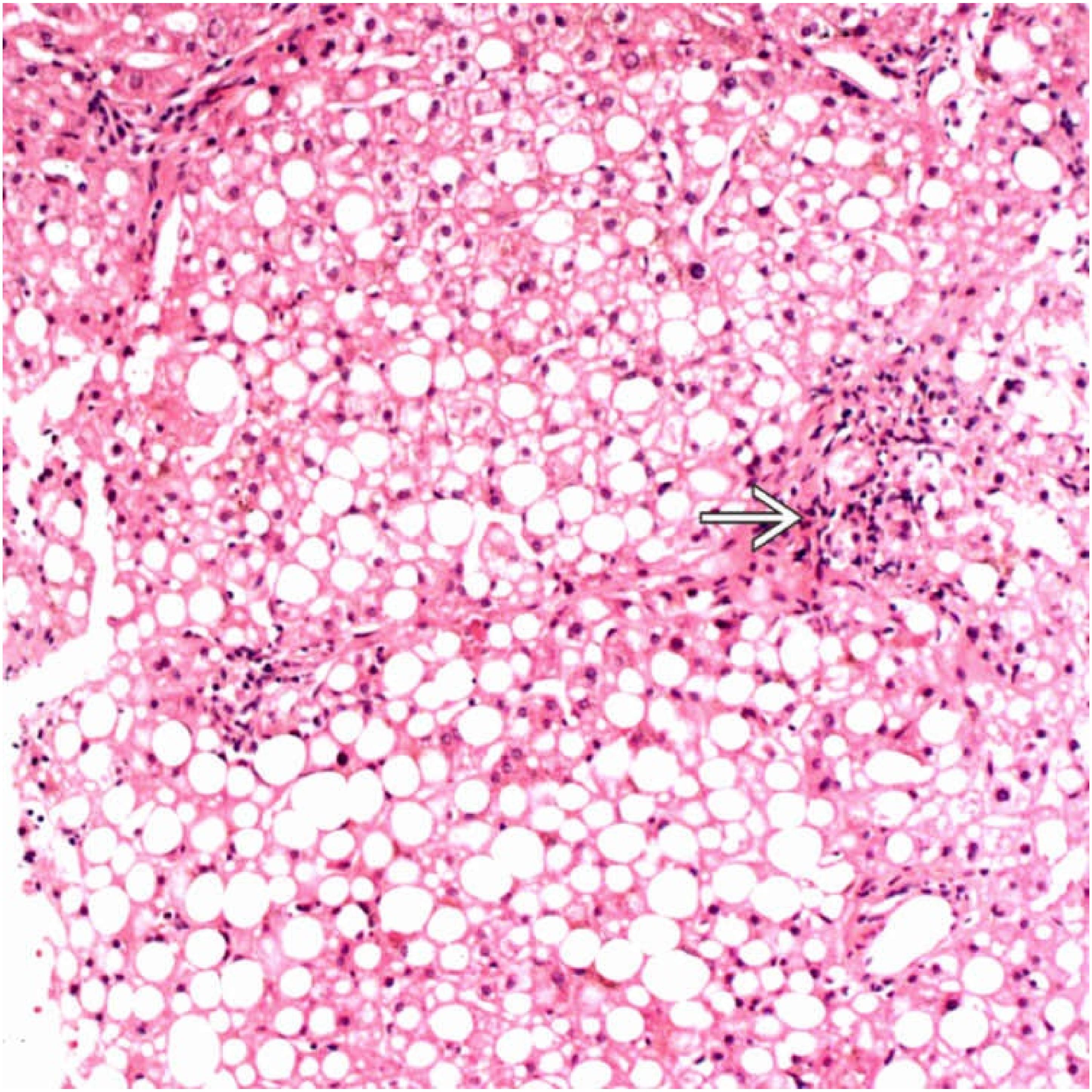
Periportal Hemosiderin in PCT

This case of PCT features subtle brown pigment granules in periportal hepatocytes ⇨ consistent with hemosiderin.

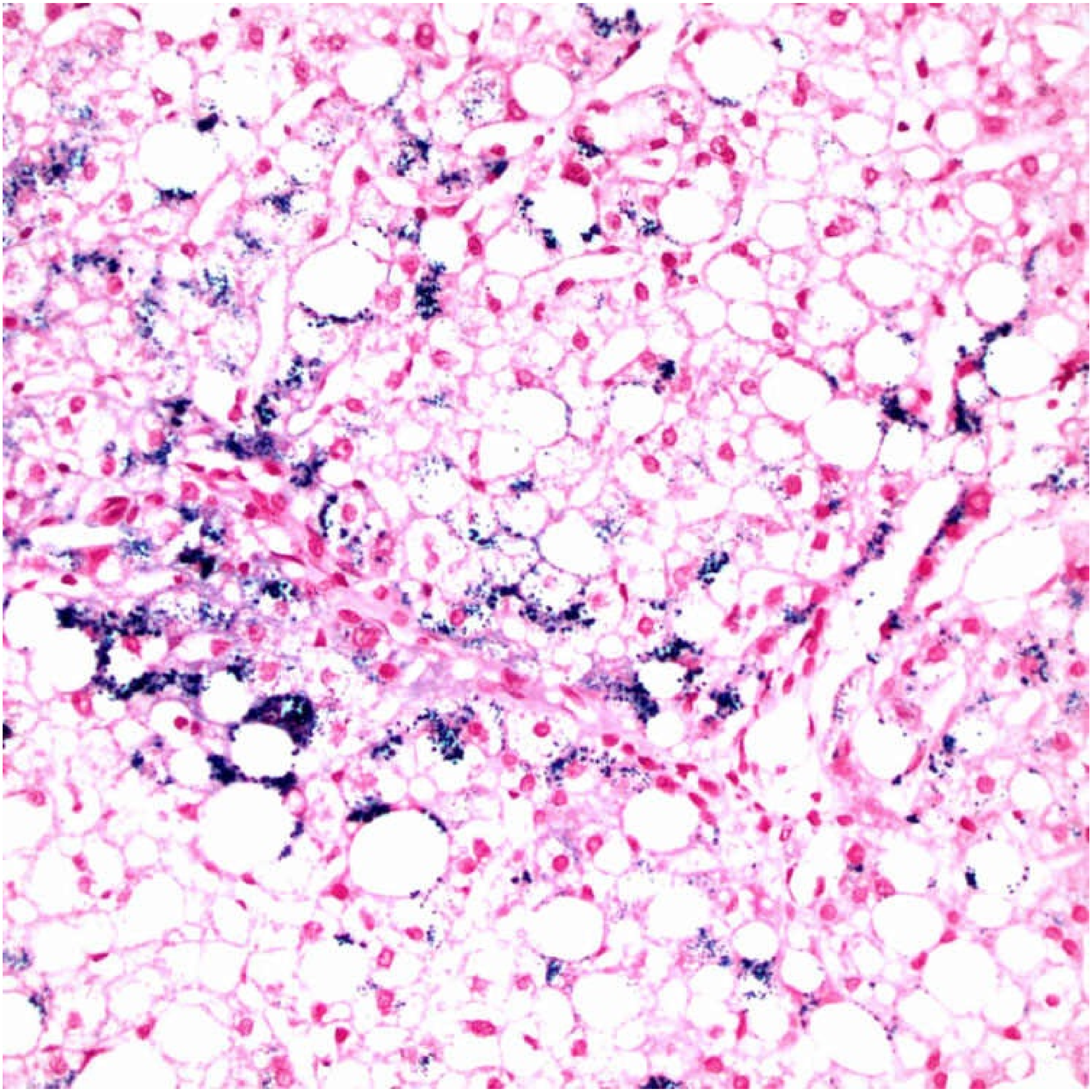


Iron Stain Shows Hemosiderin in PCT

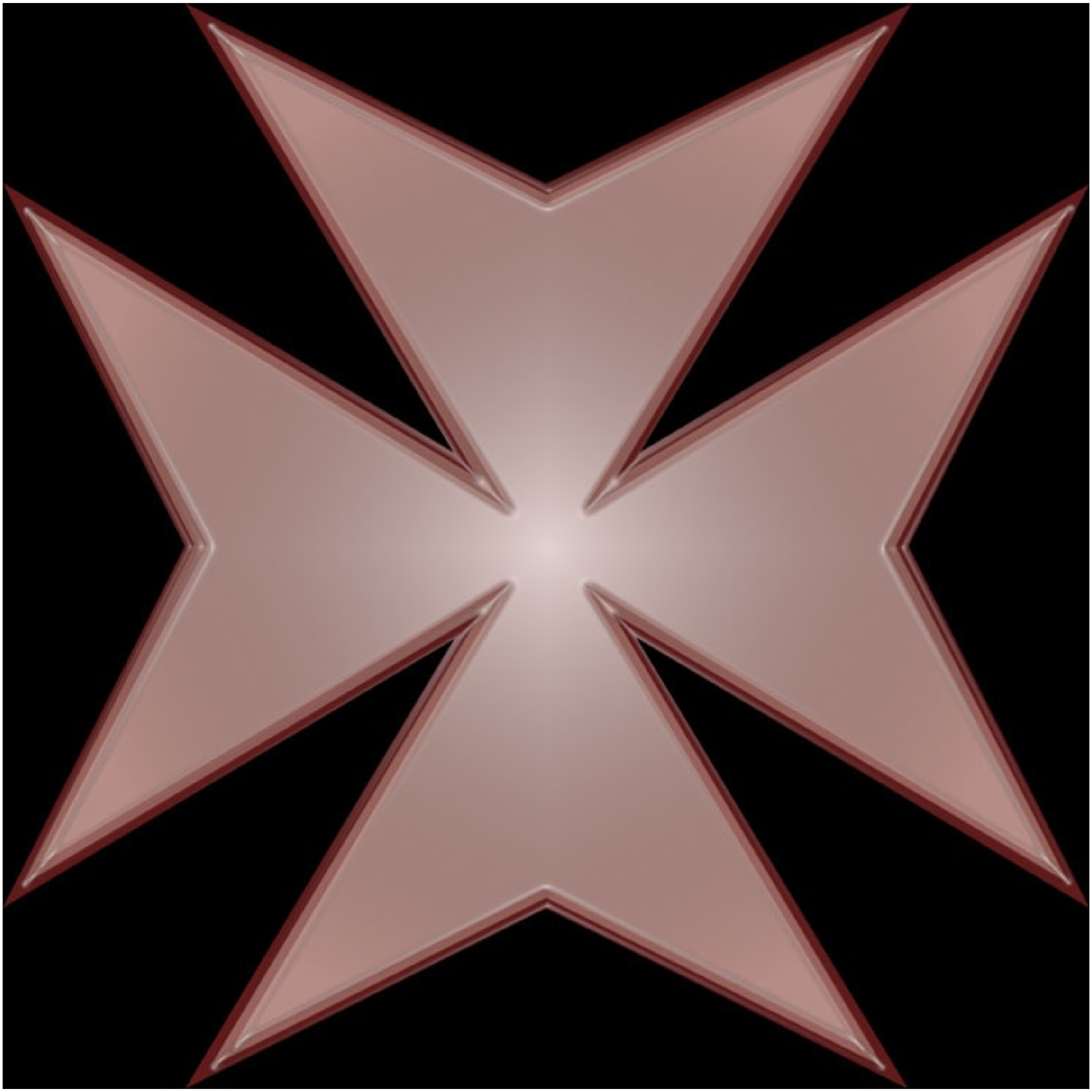
Iron stain confirms the presence of coarse blue hemosiderin deposits in periportal hepatocytes in a patient with PCT.



Steatosis and Mild Portal Inflammation in PCT
Steatosis and mild portal mononuclear infiltrates may also be seen in patients with PCT.



Periportal Hemosiderin in PCT
Iron stain demonstrates coarse periportal hemosiderin deposition in this patient with PCT.



Maltese Cross
The Maltese cross originated as the symbol of an order of Christian warriors known as the Knights of Malta and became one of the national symbols of Malta.

SELECTED REFERENCES

1. Bissell, DM, et al. Acute hepatic porphyria. *J Clin Transl Hepatol*. 2015; 3(1):17–26.
2. Karim, Z, et al. Porphyrias: A 2015 update. *Clin Res Hepatol Gastroenterol*. 2015; 39(4):412–425.
3. Gross, U, et al. Erythropoietic and hepatic porphyrias. *J Inherit Metab Dis*. 2000; 23(7):641–661.
4. Meerman, L. Erythropoietic protoporphyria. An overview with emphasis on the liver. *Scand J Gastroenterol Suppl*. 2000; 232:79–85.

5.Pimstone, NR. Hematologic and hepatic manifestations of the cutaneous porphyrias. *Clin Dermatol*. 1985; 3(2):83–102.

Dubin-Johnson Syndrome

KEY FACTS

Etiology/Pathogenesis

- Mutations in *ABCC2* (*CMOAT* / *MRP2*) gene causes impaired biliary transport of conjugated bilirubin
- Results in impaired biliary canalicular transport of organic anions including conjugated bilirubin

Clinical Issues

- Chronic or intermittent jaundice, precipitated by pregnancy or oral contraceptives
- Isolated conjugated hyperbilirubinemia
- Shift in urine coproporphyrin isomers from isomer III to isomer I
- Most patients asymptomatic
- Jaundice can be precipitated by pregnancy or by drugs that decrease hepatic excretion of organic anions (e.g., oral contraceptives)
- No treatment necessary

Macroscopic

- Grossly pigmented liver

Microscopic

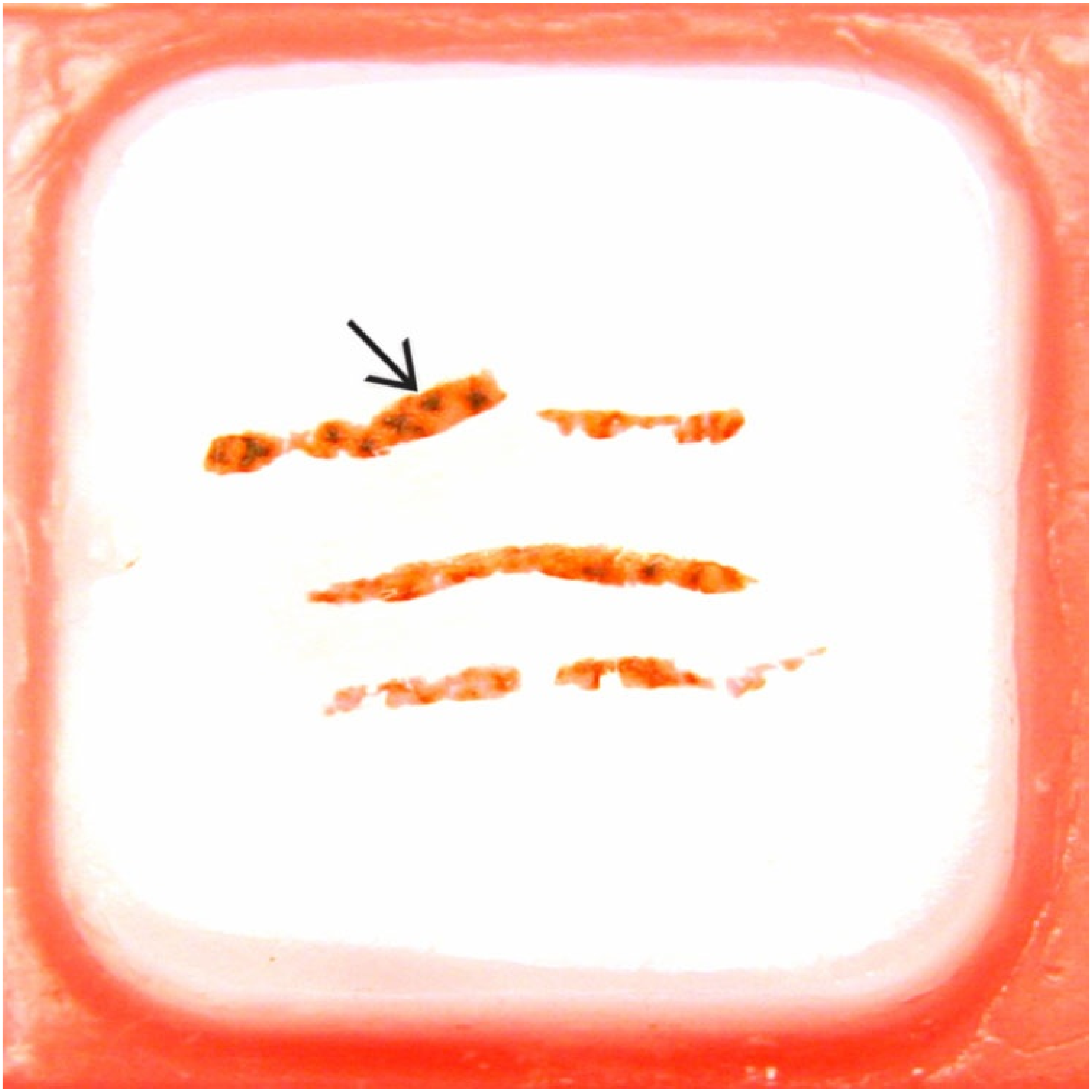
- Coarse granular pigment in centrilobular hepatocytes

Ancillary Tests

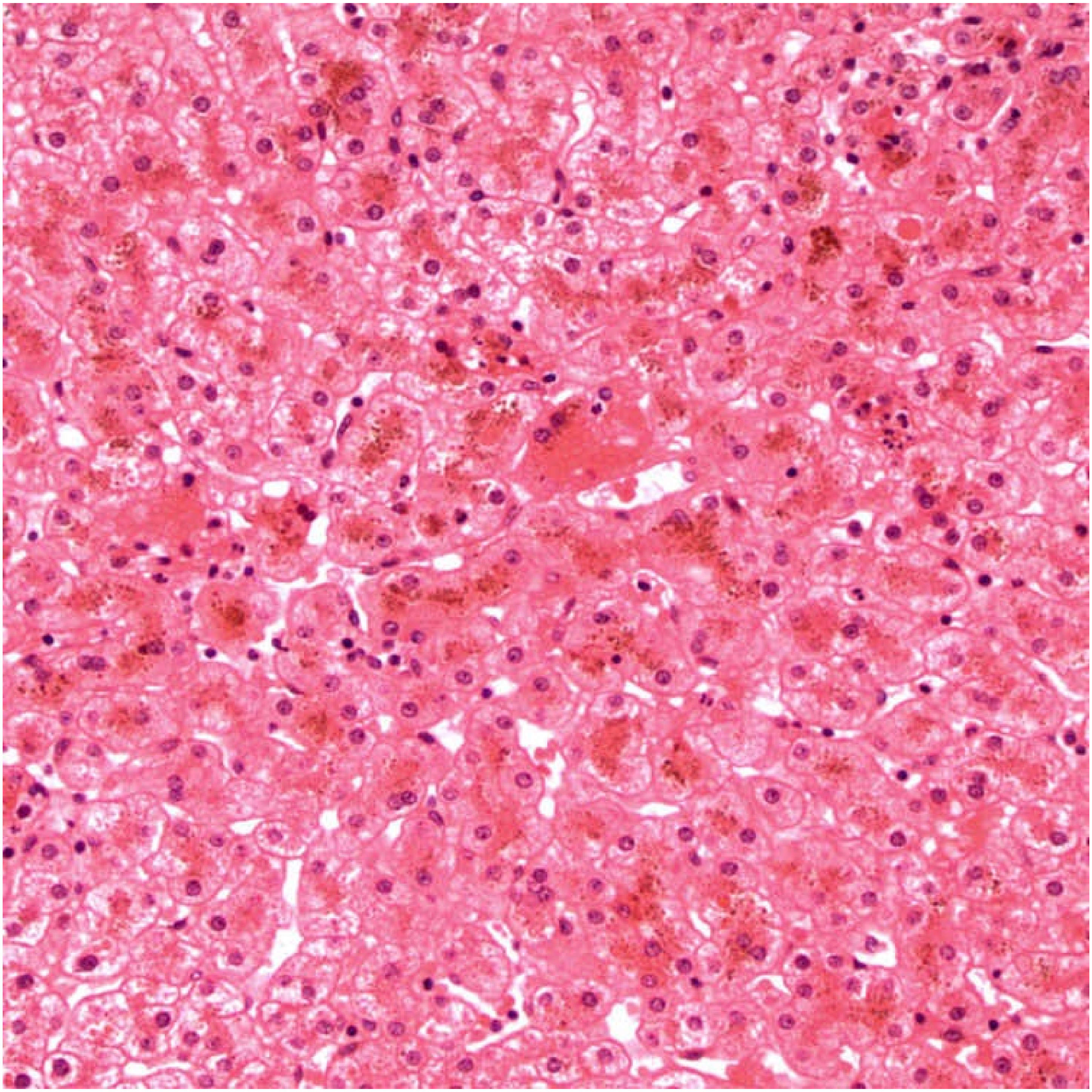
- PAS with diastase digestion and Fontana-Masson stains highlight pigment
- Absence of staining of canalicular membrane with MRP2 can help in the diagnosis
- Membrane-bound, electron-dense lysosomal granules within cytoplasm of hepatocytes

Top Differential Diagnoses

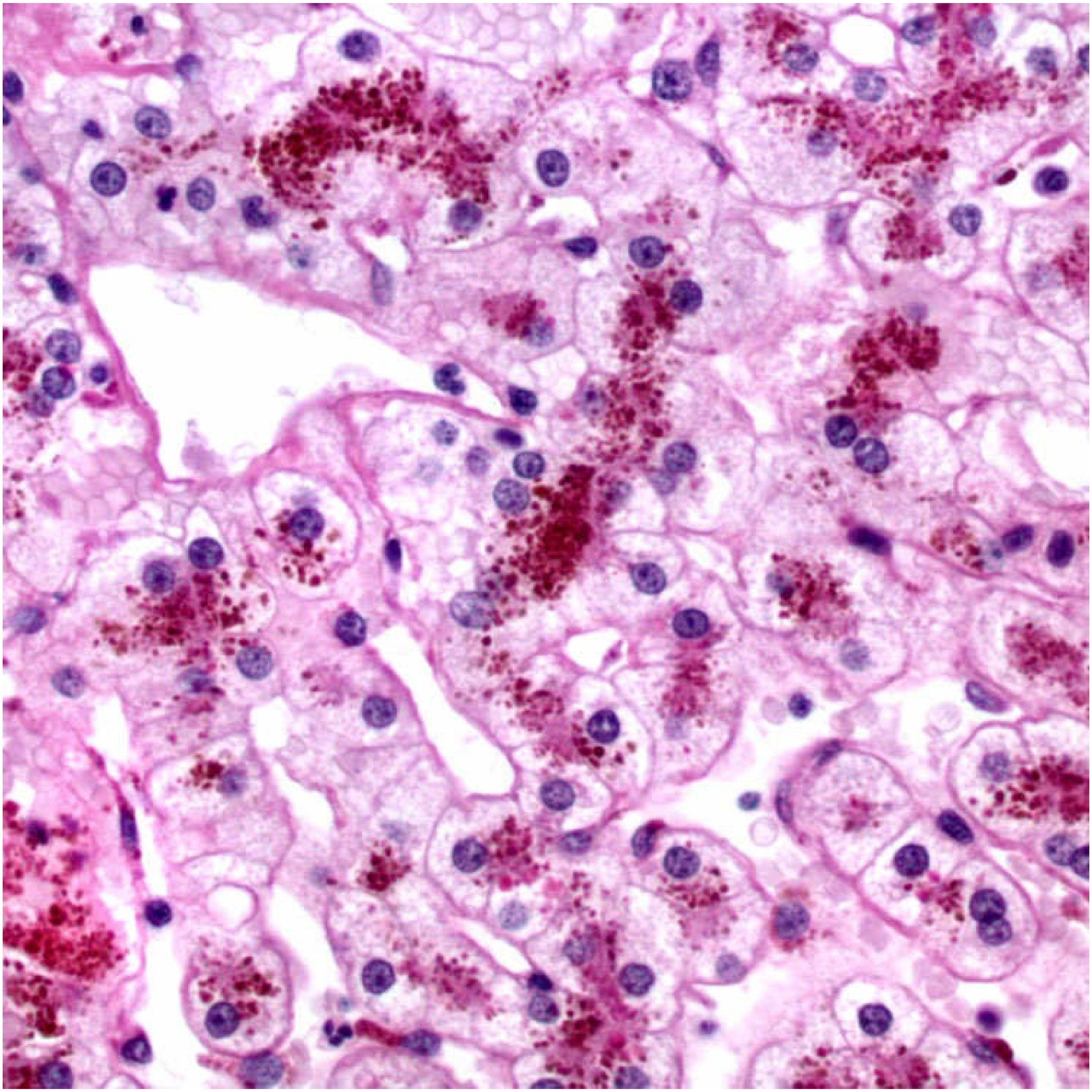
• Erythropoietic protoporphyria
• Gilbert syndrome
• Bilirubinostasis
• Hemochromatosis



Grossly Evident Pigment
Gross photograph of liver core biopsies embedded in the paraffin block show dark regions →
corresponding to the pigment within centrizonal hepatocytes.

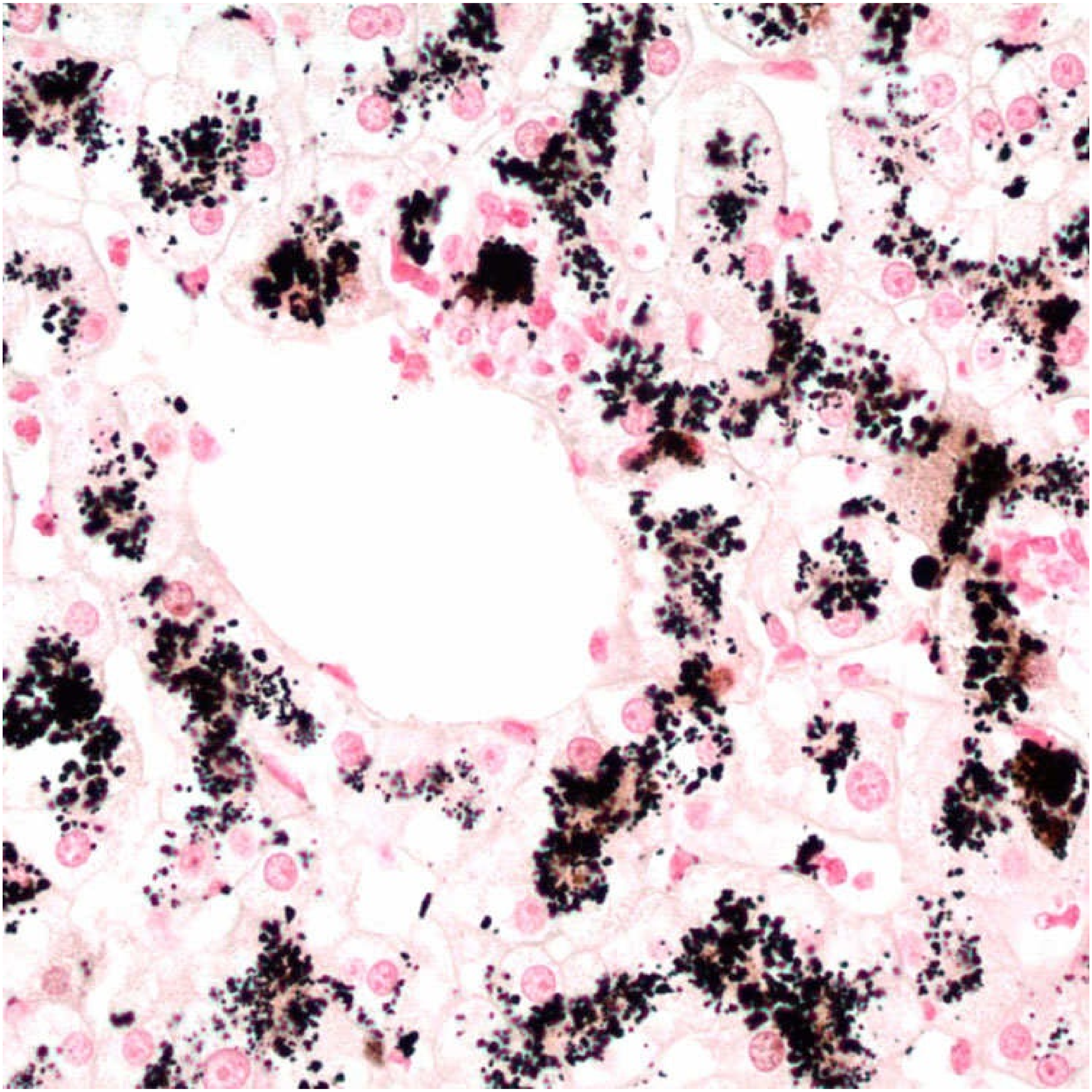


Cytoplasmic Pigment
H&E section shows coarse granular pigment deposition in centrizonal hepatocytes.



PAS Stain With Diastase Stain

PAS stain with diastase digestion accentuates the coarse pigment granules in the cytoplasm of centrizonal hepatocytes.



Fontana-Masson Stain
Fontana-Masson stain highlights the coarse pigment within centrizonal hepatocytes.

TERMINOLOGY

Definitions

• Defect in hepatocellular secretion of conjugated bilirubin

ETIOLOGY/PATHOGENESIS

Genetic Disorder

- Autosomal recessive
  - Mutations in *ABCC2* (*CMOAT* / *MRP2)* gene, which codes for ATP-dependent organic anion transport localized to canalicular membrane
  - Results in impaired biliary canalicular transport of organic anions including conjugated bilirubin
  - Impaired glutathione excretion reduces bile salt-independent bile flow

CLINICAL ISSUES

Epidemiology

- Incidence
  - Rare
- Age
  - Develop jaundice in teenage years
- Sex
  - M = F
- Ethnicity
  - Prevalence highest among Moroccan and Iranian Jews (1:1,300)

Presentation

- Most patients asymptomatic
- Can present as chronic or intermittent jaundice or with mild right upper quadrant abdominal pain
- Serum bile acids are not increased, so pruritus is absent
- Urine may be darker than normal
- Some neonates present with cholestasis
- Jaundice can be precipitated by pregnancy or by drugs that decrease hepatic excretion of organic anions (e.g., oral contraceptives)

Laboratory Tests

- Measurement of urine coproporphyrin isomers shows shift from isomer III to isomer I
- Conjugated hyperbilirubinemia
- Normal alkaline phosphatase and γ-glutamyl transpeptidase

Treatment

- No treatment necessary

Prognosis

- Excellent

MACROSCOPIC

General Features

- Grossly, liver is darkly pigmented and can appear green, slate blue, dark gray, or black

MICROSCOPIC

Histologic Features

- Coarse granular pigment in centrizonal hepatocytes
- Pigment was earlier thought to be form of melanin or lipofuscin
- Likely composed of polymers of epinephrine metabolites
- No other histologic changes

Predominant Pattern/Injury Type

- Pigment accumulation

Predominant Cell/Compartment Type

- Centrizonal region

ANCILLARY TESTS

Histochemistry

- PAS with diastase digestion
  - Accentuates cytoplasmic pigment
- Fontana-Masson
  - Silver stain that stains cytoplasmic granules black

Immunohistochemistry

- MRP2: Absence of staining of canalicular membrane
  - Available through referral centers
  - Helpful in young children whose livers have not accumulated pigment

Electron Microscopy

- Membrane-bound, electron-dense lysosomal granules within cytoplasm of hepatocytes

DIFFERENTIAL DIAGNOSIS

Erythropoietic Protoporphyria

- Can also show grossly pigmented liver but has distinct clinical and histologic features

Gilbert Syndrome

- Pigment in centrizonal hepatocytes is not as coarse
- Unconjugated hyperbilirubinemia

Bilirubinostasis

- Inspissated bile in canaliculi
- Swelling (feathery degeneration) of hepatocytes in cholestatic area

Hemochromatosis

- Prussian blue (+) pigment in periportal hepatocytes

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Coarse pigment in centrizonal hepatocytes in patient with isolated conjugated hyperbilirubinemia
- Pigment may disappear during episode of hepatitis and reaccumulate after recovery

SELECTED REFERENCES

1. Nisa, AU, et al. Dubin-Johnson syndrome. *J Coll Physicians Surg Pak*. 2008; 18(3):188–189.
2. Mor-Cohen, R, et al. Age estimates of ancestral mutations causing factor VII deficiency and Dubin-Johnson syndrome in Iranian and Moroccan Jews are consistent with ancient Jewish migrations. *Blood Coagul Fibrinolysis*. 2007; 18(2):139–144.
3. Jedlitschky, G, et al. Structure and function of the MRP2 (ABCC2) protein and its role in drug disposition. *Expert Opin Drug Metab Toxicol*. 2006; 2(3):351–366.
4. Lee, JH, et al. Neonatal Dubin-Johnson syndrome: long-term follow-up and MRP2 mutations study. *Pediatr Res*. 2006; 59(4 Pt 1):584–589.
5. Rastogi, A, et al. Dubin-Johnson syndrome–a clinicopathologic study of twenty cases. *Indian J Pathol Microbiol*. 2006; 49(4):500–504.
6. Sobaniec-Lotowska, ME, et al. Ultrastructure of Kupffer cells and hepatocytes in the Dubin-Johnson syndrome: a case report. *World J Gastroenterol*. 2006; 12(6):987–989.

Gilbert Disease

KEY FACTS

Terminology

- Inherited unconjugated hyperbilirubinemia due to mutation of promoter of *B-UGT* gene

Etiology/Pathogenesis

- Decreased transcription of *UGT1A1* gene results in decreased conjugation of bilirubin
- Extra TA in TATAA box of *UGT1A1* promoter (this variant is known as B-UGT*28)
- Decreased transcription of gene to 20% of normal
- Decreased conjugation of some drugs (irinotecan, atazanavir, TAS-103, indinavir, tolbutamide, rifamycin)

Clinical Issues

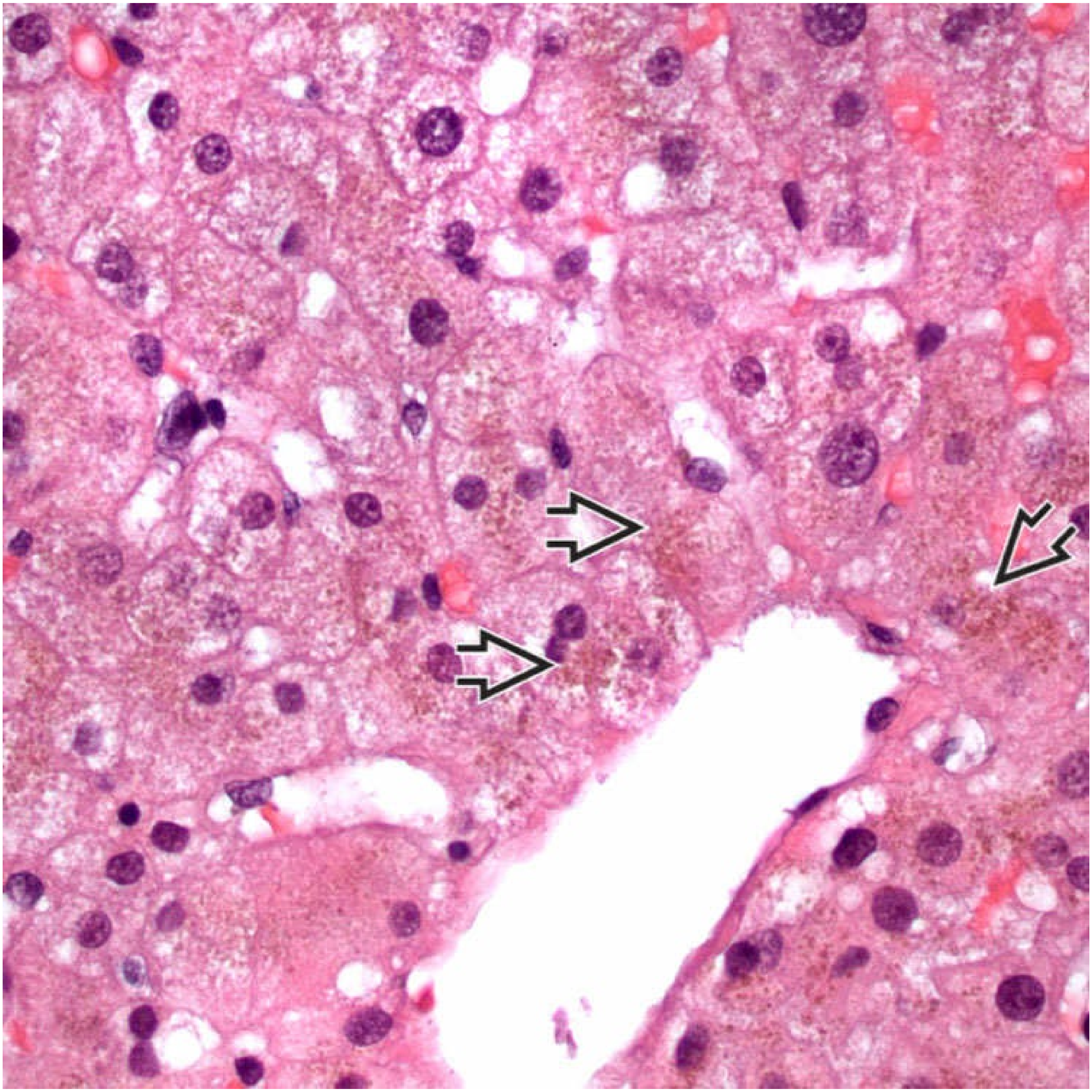
- Up to 16% of population may be homozygous
- No treatment necessary
- Decreased conjugation of some drugs results in increased risk of adverse effect to those drugs
- Mild unconjugated nonhemolytic hyperbilirubinemia, usually fluctuating and < 3 mg/dL
- Higher bilirubin can occur during illness, stress, or menstrual period

Microscopic

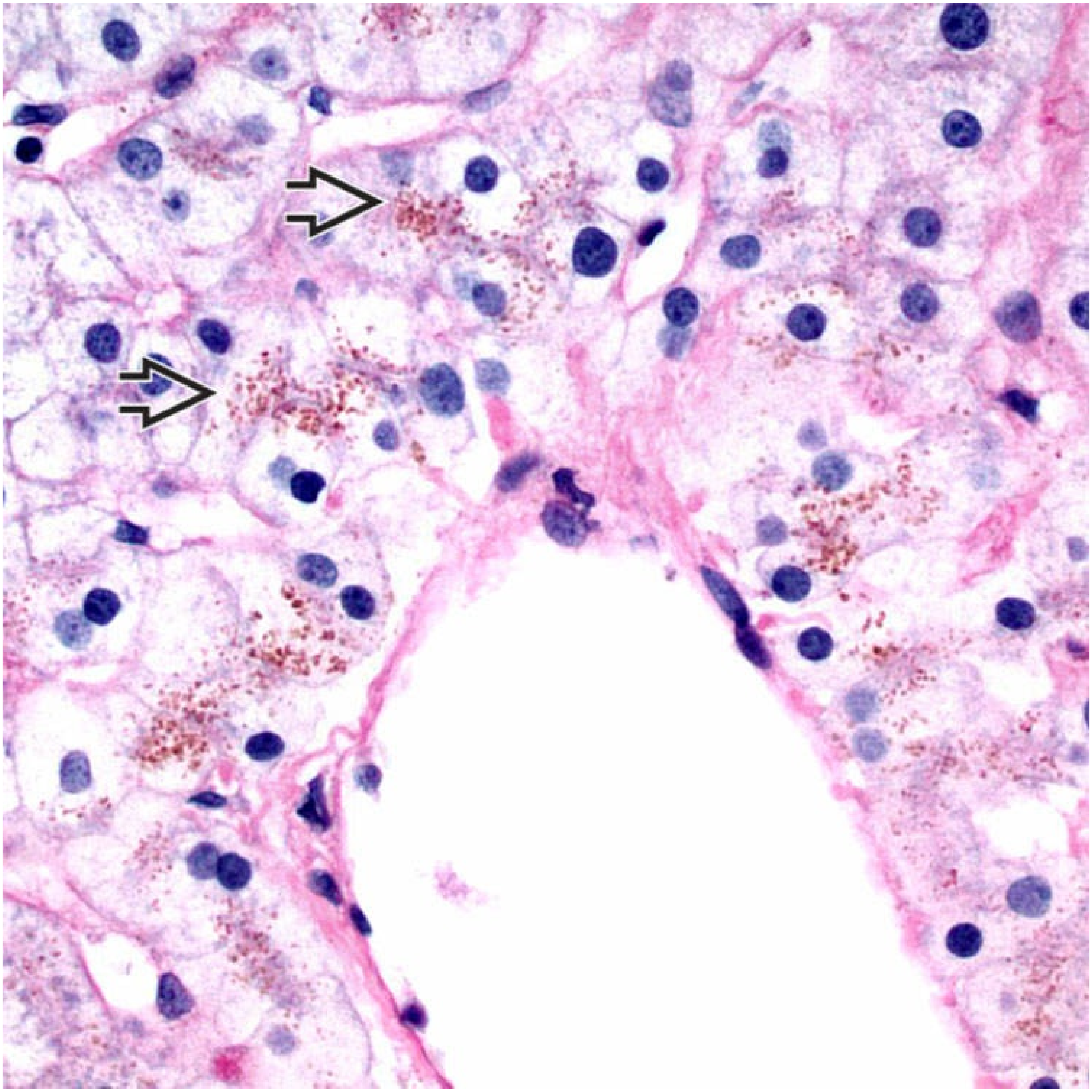
- Increased lipofuscin in zone 3
- No inflammation, hepatocellular injury, or fibrosis

Top Differential Diagnoses

- Lipofuscin deposition
- Dubin-Johnson syndrome
- Crigler-Najjar, types 1 and 2

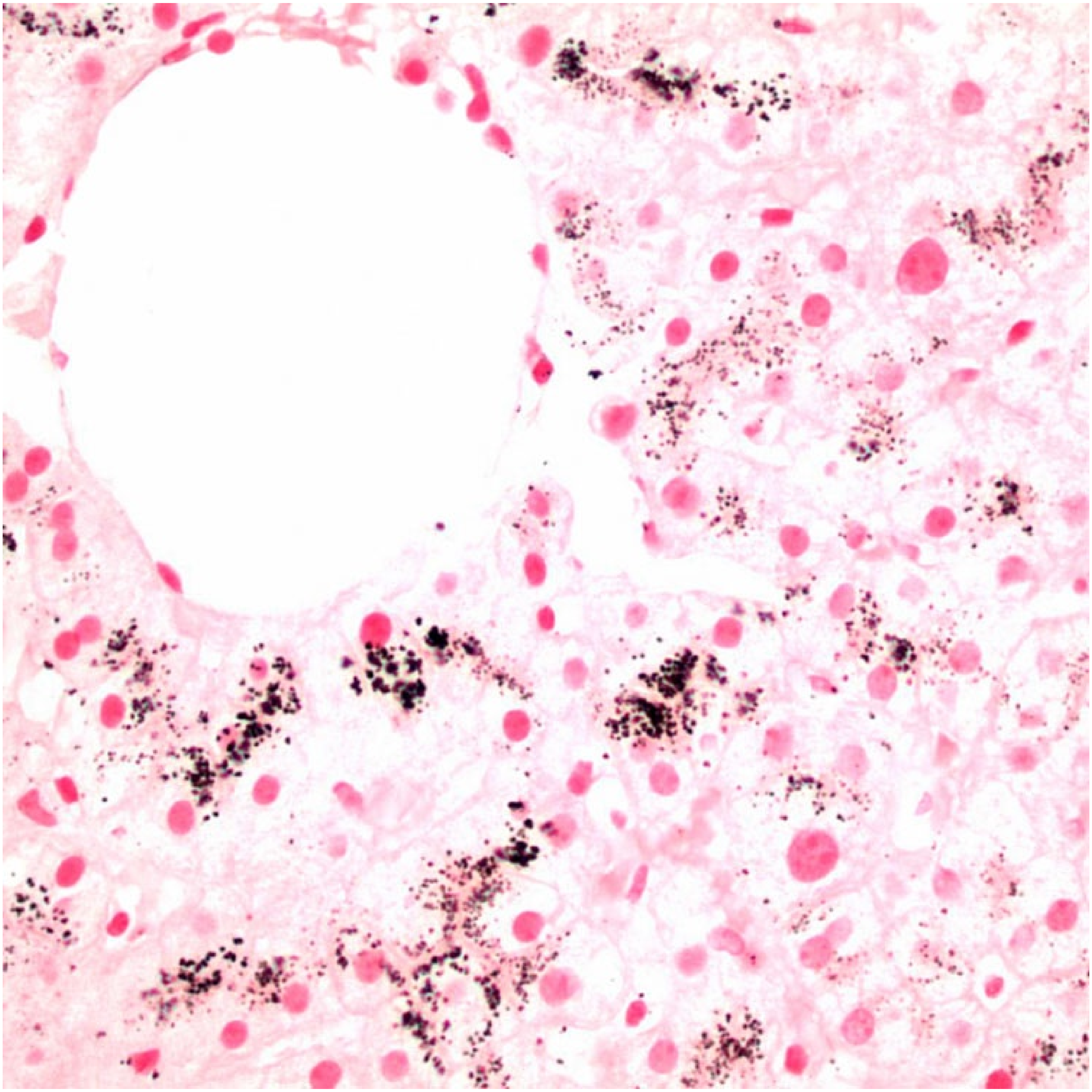


Cytoplasmic Pigment
H&E at high power shows lipofuscin pigment ➩ in centrizonal hepatocytes.

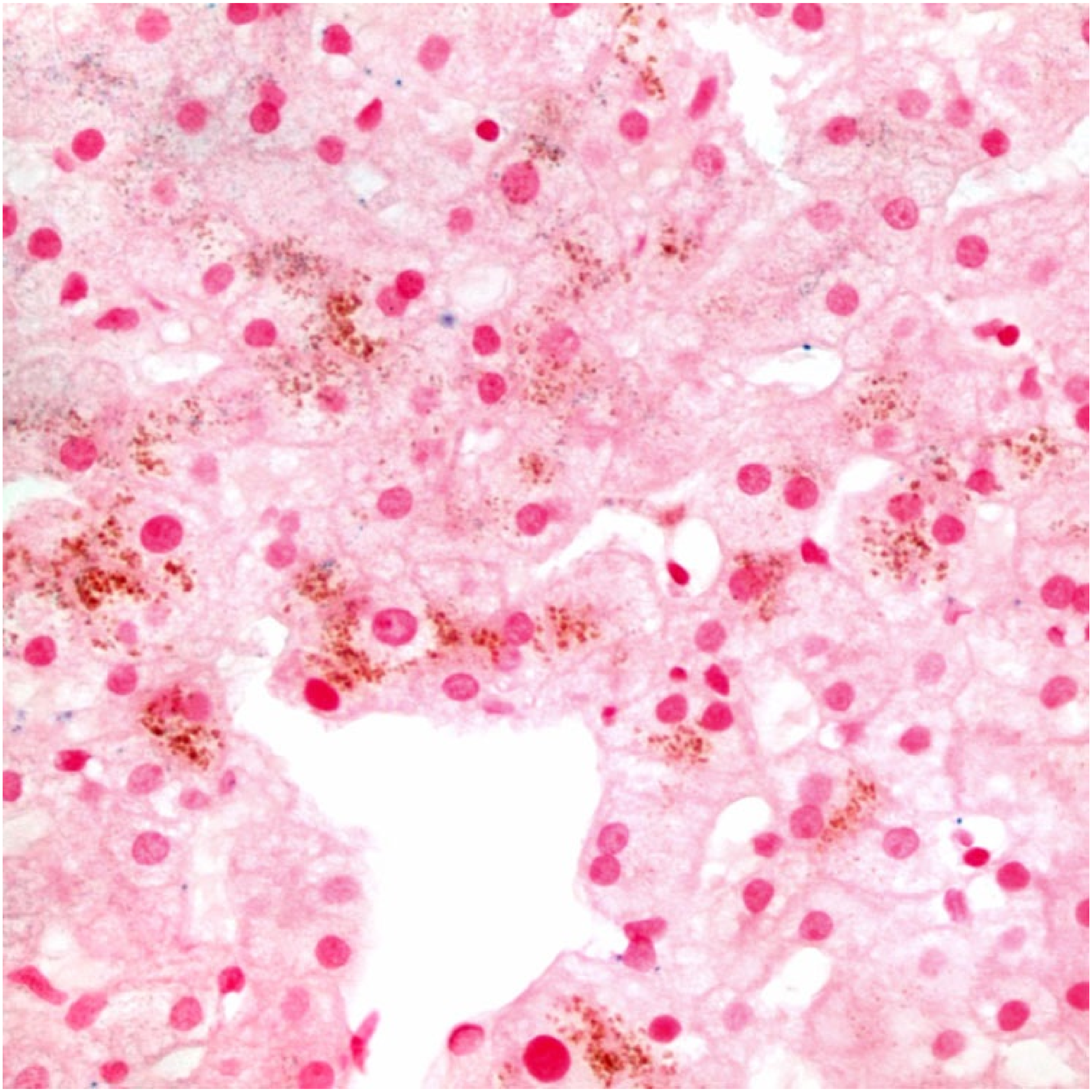


PAS-D Stain

Periodic acid-Schiff with diastase digestion accentuates the granular pigment in centrizonal hepatocytes , even though the pigment is not PAS-D positive.



Fontana-Masson Stain
Fontana-Masson stain highlights the increased lipofuscin marked by black staining in the centrizonal hepatocytes.



Iron Stain
Prussian blue stain for iron is negative and helps to confirm that the cytoplasmic pigment is not hemosiderin.

TERMINOLOGY

Definitions

- Inherited unconjugated hyperbilirubinemia due to mutations of bilirubin uridine diphosphate glucuronosyltransferase (B-UGT or *UGT1A1*) gene

ETIOLOGY/PATHOGENESIS

Genetic Disorder

- Extra TA in TATAA box of *UGT1A1* promoter (this variant is known as B-UGT*28)
  - Decreased transcription of gene to 20% of normal
  - – Decreased conjugation of bilirubin with glucuronic acid
  - – Decreased conjugation of some drugs (irinotecan, atazanavir, TAS-103, indinavir, tolbutamide, rifamycin)
- Affected patients typically have 2nd condition causing increased bilirubin load
  - Examples of additional condition include reduced red blood cell lifespan or impaired hepatic bilirubin uptake

CLINICAL ISSUES

Epidemiology

- Incidence
  - Among Caucasians, mutation has frequency of 35-40%
  - – 11-16% of population homozygous
- Age
  - Often diagnosed at puberty, possibly related to increased hemoglobin turnover and inhibition of bilirubin glucuronidation by endogenous steroid hormones
- Sex
  - Males affected more than females, possible due to higher rate of bilirubin production in males

Presentation

- Mild unconjugated nonhemolytic hyperbilirubinemia, usually fluctuating and < 3 mg/dL
  - Higher bilirubin can occur during illness, stress, or menstrual period
  - Otherwise normal liver function
  - Jaundice is only finding on physical examination
  - Associated with prolonged neonatal jaundice and development of gallstones in patients with hereditary spherocytosis
  - Associated with increased risk of toxicity from drugs metabolized by B-UGT
  - Irinotecan has been associated with severe diarrhea and neutropenia
  - Increased risk of hyperbilirubinemia with atazanavir

Laboratory Tests

- Mild unconjugated hyperbilirubinemia
- Normal alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase
- Increased proportion of bilirubin monoglucuronide in bile
- Rifampin administration causes disproportionate unconjugated hyperbilirubinemia relative to normal patients
- Caloric restriction causes disproportionate unconjugated hyperbilirubinemia relative to normal patients

Treatment

- No treatment necessary

Prognosis

- Excellent

MACROSCOPIC

General Features

- No macroscopic findings

MICROSCOPIC

Histologic Features

- Increased lipofuscin in centrizonal hepatocytes

Predominant Pattern/Injury Type

- Pigment accumulation

Predominant Cell/Compartment Type

- Hepatocyte

DIFFERENTIAL DIAGNOSIS

Lipofuscin Deposition

- Increased lipofuscin can be seen in advancing age, chronic drug ingestion, and as variant of normal

Dubin-Johnson Syndrome

- Pigment is considerably more coarse

Crigler-Najjar, Types 1 and 2

- Severe unconjugated hyperbilirubinemia characterized by total or near-total absence of B-UGT activity
- Mutations in exons 1-5 of *UGT1A1* gene
- Biopsy can show cholestasis or appear normal

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Does not lead to liver inflammation, fibrosis, cirrhosis, or liver failure
- Testing for B-UGT*28 often done to identify patients at risk for certain drug toxicities and to tailor dose

Pathologic Interpretation Pearls

- Increased lipofuscin in centrizonal hepatocytes

SELECTED REFERENCES

1. Ehmer, U, et al. Rapid allelic discrimination by TaqMan PCR for the detection of the Gilbert's syndrome marker UGT1A1*28. *J Mol Diagn*. 2008; 10(6):549–552.
2. Costa, E. Hematologically important mutations: bilirubin UDP-glucuronosyltransferase gene mutations in Gilbert and Crigler-Najjar syndromes. *Blood Cells Mol Dis*. 2006; 36(1):77–80.
3. Hallal, H, et al. A shortened, 2-hour rifampin test: a useful tool in Gilbert's syndrome. *Gastroenterol Hepatol*. 2006; 29(2):63–65.
4. Erdil, A, et al. Rifampicin test in the diagnosis of Gilbert's syndrome. *Int J Clin Pract*. 2001; 55(2):81–83.
5. Ishihara, T, et al. Role of UGT1A1 mutation in fasting hyperbilirubinemia. *J Gastroenterol Hepatol*. 2001; 16(6):678–682.
6. Kadakol, A, et al. Genetic lesions of bilirubin uridine-diphosphoglucuronate glucuronosyltransferase (UGT1A1) causing Crigler-Najjar and Gilbert syndromes: correlation of genotype to phenotype. *Hum Mutat*. 2000; 16(4):297–306.

Progressive Familial Intrahepatic Cholestasis

KEY FACTS

Etiology/Pathogenesis

- PFIC1 (FIC1 disease) is due to mutations of *ATP8B1* (FIC1) gene
- PFIC2 (BSEP disease) is due to mutations of *ABCB11* gene that encodes bile salt export pump
- PFIC3 is due to mutation of *ABCB4* gene that encodes MDR3, a phospholipid flippase

Clinical Issues

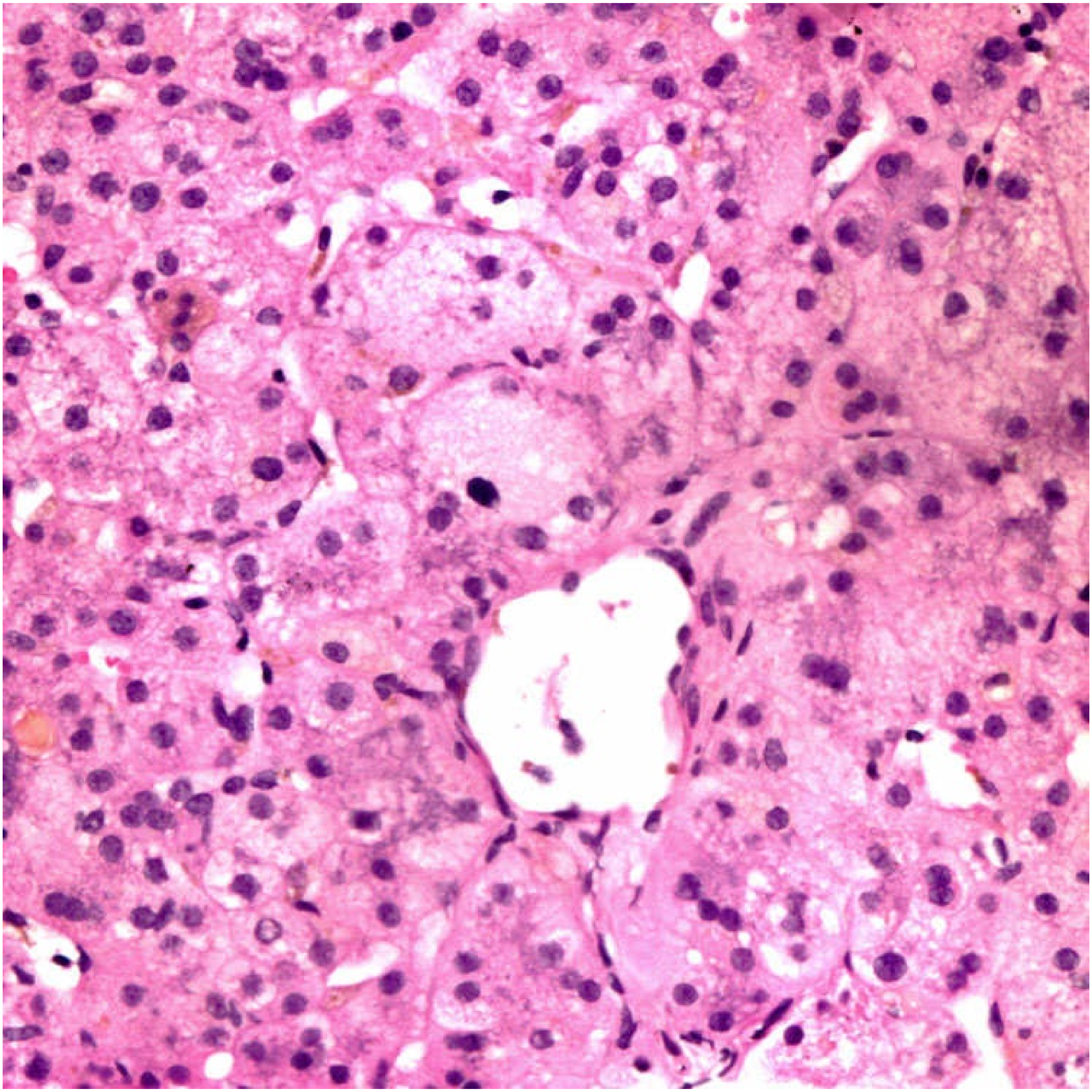
- PFIC presents in 1st year of life with intense pruritus and jaundice
- PFIC1 and PFIC2 are characterized by normal serum GGT, whereas PFIC3 is associated with elevated GGT
- Progressive forms lead to liver failure, cirrhosis, and death before adulthood
- Partial external biliary diversion or ileal exclusion may be used with some success, but most patients require liver transplantation

Microscopic

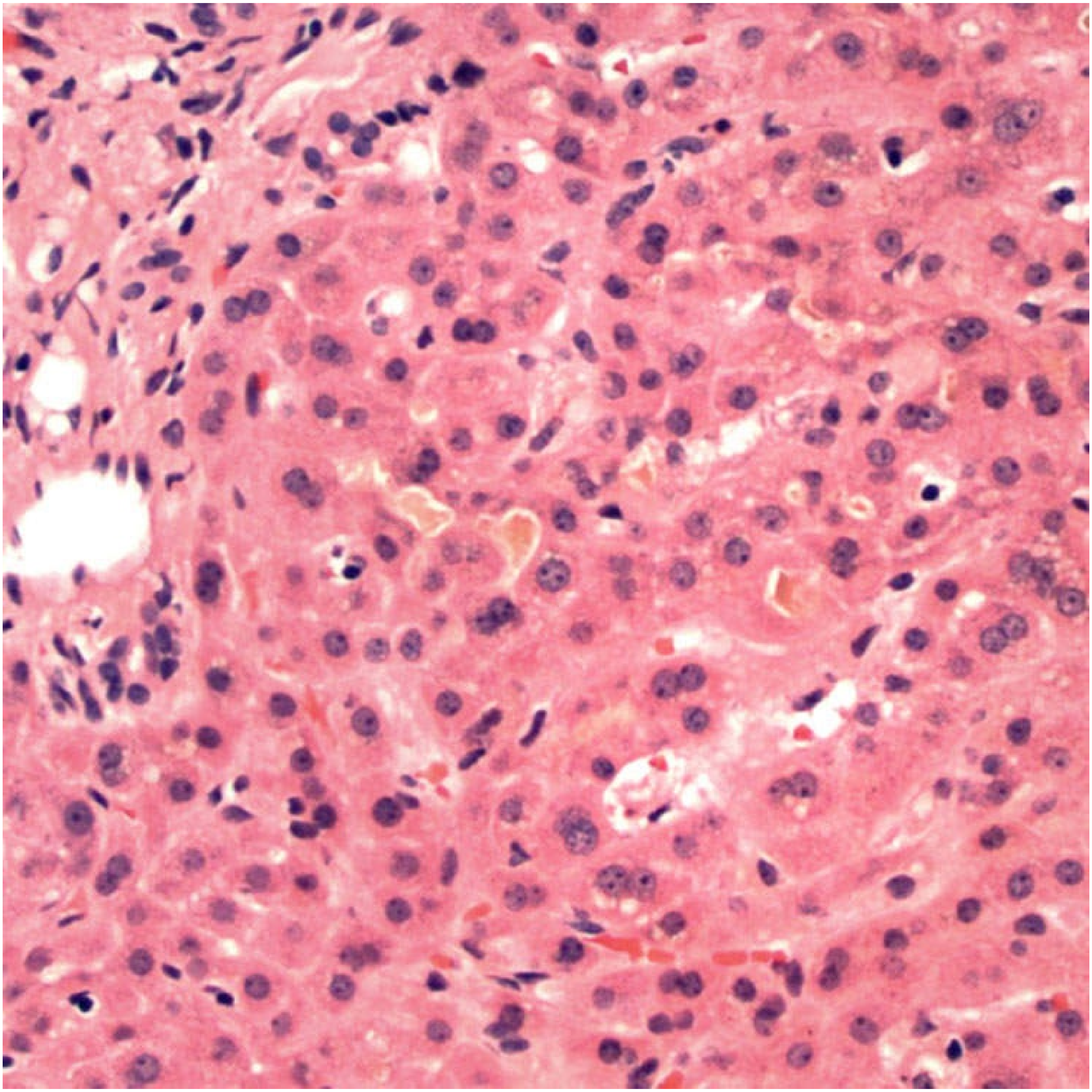
- PFIC1 is characterized by relatively bland canalicular cholestasis
- PFIC2 is characterized by pattern of neonatal giant cell hepatitis
- PFIC3 is characterized by ductular reaction and bile plugs in ductules
- Preserved immunostainings of BSEP and MDR3 do not exclude PFIC

Ancillary Tests

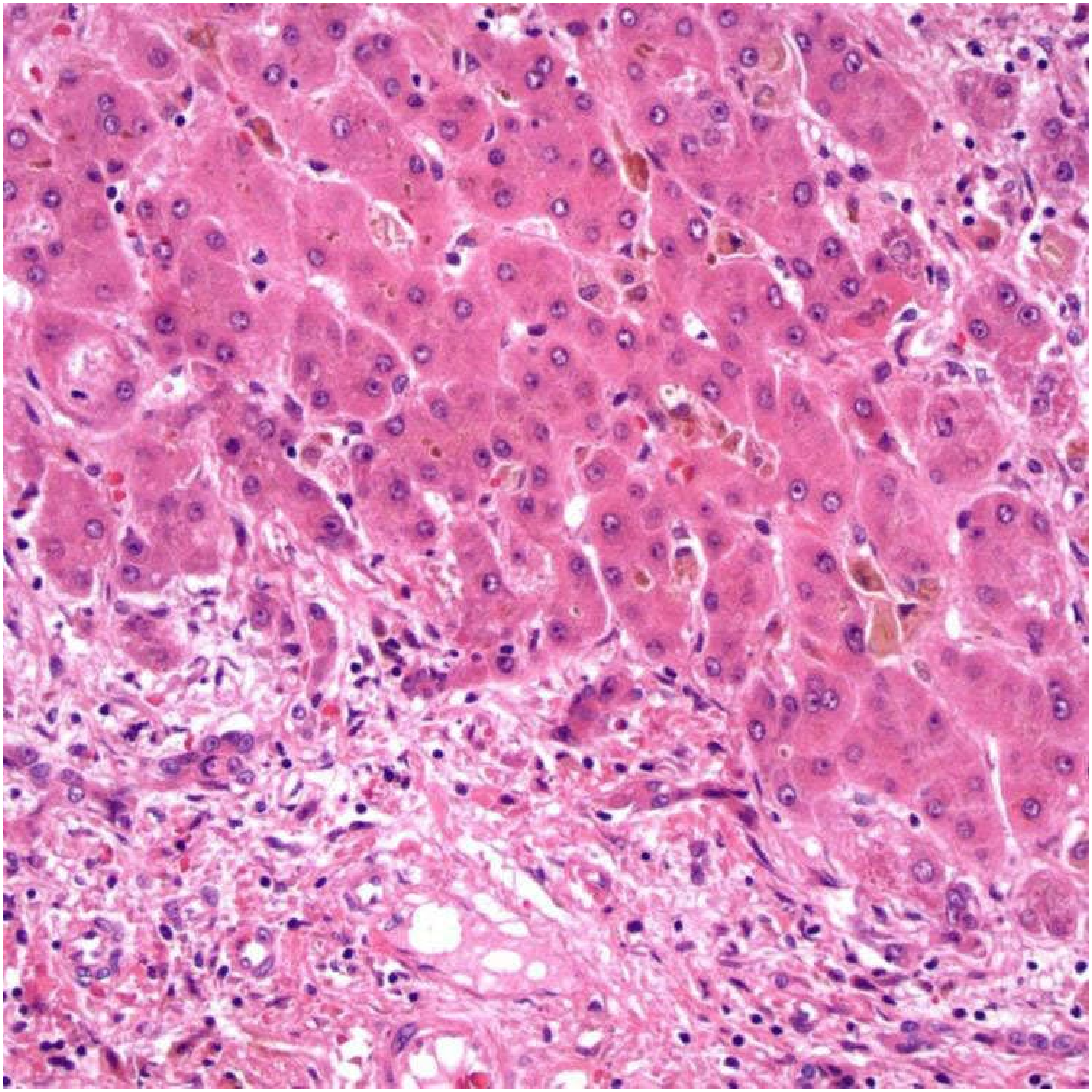
- FIC1 disease reveals coarse, granular bile, referred to as Byler bile
- Immunohistochemistry for canalicular proteins can be used for diagnosis



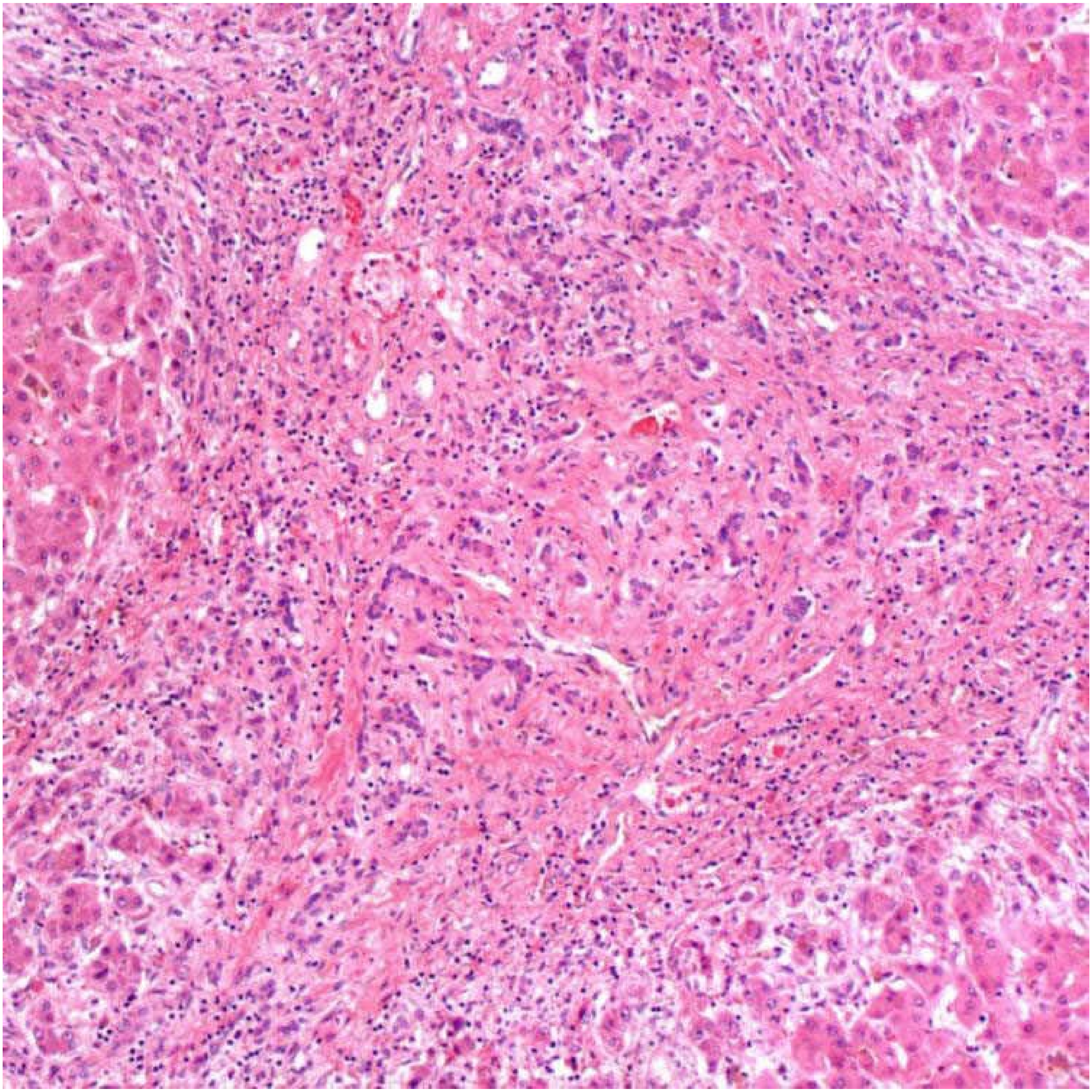
Giant Cell Transformation
H&E-stained section of a liver biopsy in a child with progressive familial intrahepatic cholestasis (PFIC) shows giant cell transformation of perivenular hepatocytes, typical of childhood cholestasis syndromes.



Bland Canalicular Cholestasis
H&E-stained section of a liver biopsy in an adult patient with benign recurrent intrahepatic cholestasis (BRIC) shows bland canalicular cholestasis with mild lobular architectural disarray but minimal inflammation.



Periportal Cholestasis
H&E-stained section of a liver biopsy in a patient with PFIC1 shows periportal cholestasis and bile ductular reaction in the portal tract.



Fibrous Septa
H&E-stained section of a liver explant in a patient with PFIC1 shows periseptal cholestasis, intrahepatocytic clearing, and bile ductular reaction in the fibrous septa.

TERMINOLOGY

Abbreviations

- Progressive familial intrahepatic cholestasis (PFIC)

Synonyms

- PFIC type 1

- Familial intrahepatic cholestasis 1 (FIC1) disease
- Byler disease, Byler syndrome
- Greenland familial cholestasis (GFC)

- PFIC type 2
  - Bile salt export pump (BSEP) disease
- PFIC type 3
  - Multidrug resistance protein 3 (MDR3) disease

Definitions

- Heterogeneous group of autosomal recessive disorders characterized by chronic cholestasis and progression to cirrhosis and liver failure

ETIOLOGY/PATHOGENESIS

Autosomal Recessive Genetic Disorder

- PFIC1
  - Mutation of *ATP8B1* (FIC1) gene, located on chromosome 18q21-q22
  - – FIC1 is expressed on variety of tissues including liver, intestine, pancreas
  - – Functions as aminophospholipid flippase, flipping phosphatidylserine from outer to inner lipid layer of cell membrane
  - – Mechanism of cholestasis unclear
- PFIC2
  - Mutations of *ABCB11* gene on chromosome 2q24 that encodes BSEP, an ATP-dependent bile acid transporter on canalicular membrane
- PFIC3
  - Mutation of *ABCB4* gene that encodes MDR3 glycoprotein
    - – MDR3 is flippase that flips phosphatidylcholine from inner to outer lipid leaflet of canalicular membrane
    - – Phosphatidylcholine in bile reduces its detergent action, and MDR3 deficiency results in bile with more detergent properties
    - – Absence of phospholipids destabilizes micelles, promoting lithogenicity of bile with crystallization of cholesterol and leads to small bile duct obstruction

CLINICAL ISSUES

Presentation

- FIC1 deficiency disease
  - Depending on nature of mutation, may present as benign recurrent intrahepatic cholestasis (BRIC1) or progressive and severe form (PFIC1)
  - PFIC1
  - – Presents in 1st year of life with intense pruritus and jaundice
  - – Systemic disorder with extrahepatic manifestations including pancreatitis, diarrhea, respiratory

symptoms, failure to thrive, delayed sexual development, hearing loss

- BRIC1
  - Recurrent episodes of cholestasis with intense pruritus
  - Episodes resolve spontaneously without histologic progression

- BSEP disease
  - Depending on nature of mutation, may present as BRIC2 or PFIC2
  - PFIC2
    - Presents as severe intrahepatic cholestasis in infancy
  - BRIC2
    - Presents as recurrent episodes of pruritus, steatorrhea, nausea, vomiting, anorexia, right upper quadrant abdominal pain, and weight loss
    - Frequently complicated by cholesterol cholelithiasis
- MDR3 disease
  - PFIC3 presents during infancy with pruritus, jaundice, pale stools, hepatomegaly, or complications of portal hypertension, such as splenomegaly or gastrointestinal bleeding
  - MDR3 mutations also seen in patients with intrahepatic lithiasis, cholesterol gallstone disease, intrahepatic cholestasis of pregnancy, transient neonatal cholestasis, cholestatic drug reactions

Laboratory Tests

- GGT
  - Normal in PFIC1 and PFIC2
  - Elevated in PFIC3
- Elevated serum bile acids in all 3 types
- PFIC3 is characterized by low concentrations of phospholipids in bile analysis

Natural History

- Progressive forms can result in worsening hepatic function, liver failure, cirrhosis, and death before adulthood
  - Chronic cholestasis leads to complications of fat malabsorption such as deficiencies of fat-soluble vitamins and weight loss
- BSEP disease is associated with development of hepatocellular carcinoma

Treatment

- Surgical approaches
  - Partial external biliary diversion or cholecystojejunocutaneostomy
  - Short jejunal segment is anastomosed to the dome of gallbladder and terminates as stoma, allowing bile to be discarded

- Ileal exclusion
  - ~ 15% of terminal ileum is bypassed, which reduces bile acid reabsorption

○ Liver transplantation
– May result in intractable diarrhea and steatohepatitis in FIC1 patients
• Drugs
  ○ Ursodeoxycholic acid (UDCA), rifampin, cholestyramine, and phenobarbital have been used to treat pruritus

MICROSCOPIC

Histologic Features

• FIC1 disease
  ○ BRIC1
  – Bland canalicular cholestasis with variable cholestatic rosettes, compact hepatocytes, hepatocyte multinucleation without prominent giant cell transformation
  – Minimal inflammation
○ PFIC1: Increasing portal fibrosis with eventual cirrhosis
– Pattern of fibrosis that involves early pericentral sclerosis, central-to-portal fibrosis, and cirrhosis with lacy lobular fibrosis has been described
○ Bile duct injury and paucity may be present as well as bile ductular reaction
• BSEP disease
  ○ Neonatal hepatitis pattern with giant cell transformation, swelling, inflammation, and canalicular cholestasis
  ○ Bile duct injury and paucity may be present as well as bile ductular reaction
  ○ PFIC2 shows increasing fibrosis and eventual cirrhosis
    – Pattern of fibrosis that involves early pericentral sclerosis, central-to-portal fibrosis, and cirrhosis with lacy lobular fibrosis has been described
• MDR3 disease
  ○ Expanded portal tracts with ductular proliferation and mixed inflammatory infiltrates
  ○ Cholestasis and giant cell transformation of hepatocytes may be seen
  ○ Late stages characterized by biliary cirrhosis, bile plugs in ductules, and interlobular bile ducts without periductal fibrosis or epithelial injury
  ○ May see cholesterol clefts in bile ducts

ANCILLARY TESTS

Immunohistochemistry

• FIC1 disease shows diffuse variable reduction in canalicular expression of CDT3, GGT, and pCEA
• BSEP disease shows absent canalicular staining for BSEP but preserved staining for other canalicular enzymes such as pCEA

- MDR3 disease shows absent canalicular staining for MDR3 but preserved staining for other canalicular proteins such as pCEA and BSEP
- Preserved immunostainings of BSEP and MDR3 do not exclude PFIC

Electron Microscopy

- FIC1 disease reveals coarse, granular bile, referred to as Byler bile
- MDR3 disease may show cholesterol clefts in bile ducts or canaliculi

DIFFERENTIAL DIAGNOSIS

Bile Acid Synthesis Defect

- Also shows low GGT, but unlike PFIC, serum bile acid concentration is low

Biliary Atresia

- Histology shows obstructive pattern with bile ductular reaction, inspissated bile in ducts
- Hepatobiliary imaging confirms atretic bile duct

Other Childhood Cholestatic Disorders

- Histology of many cholestatic childhood disorders is indistinguishable from PFIC, and their distinction requires wide array of serologic, biochemical, and genetic tests

Primary Sclerosing Cholangitis

- Histology shows periductal fibrosis
- Cholangiogram shows strictures and dilatations

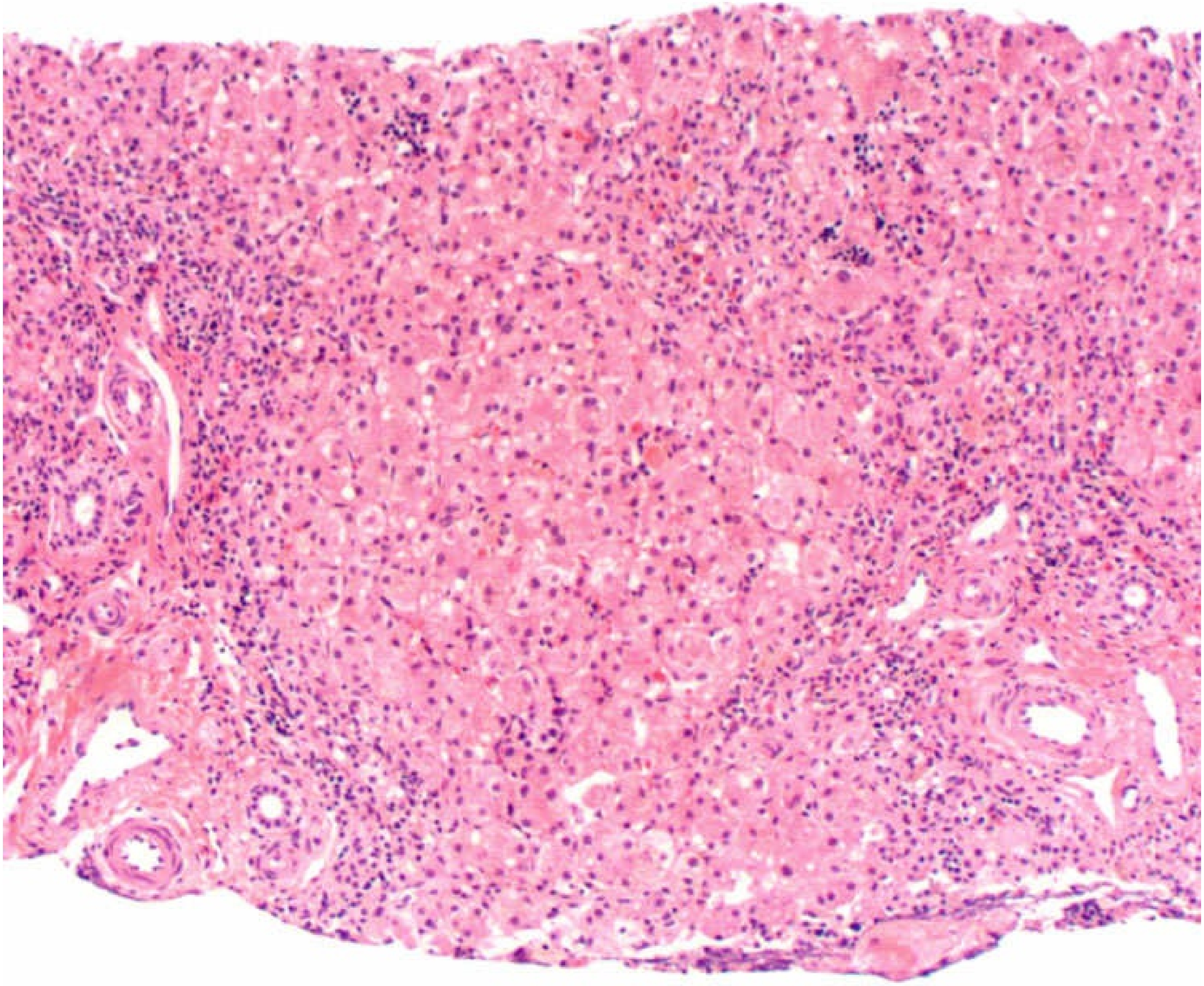
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

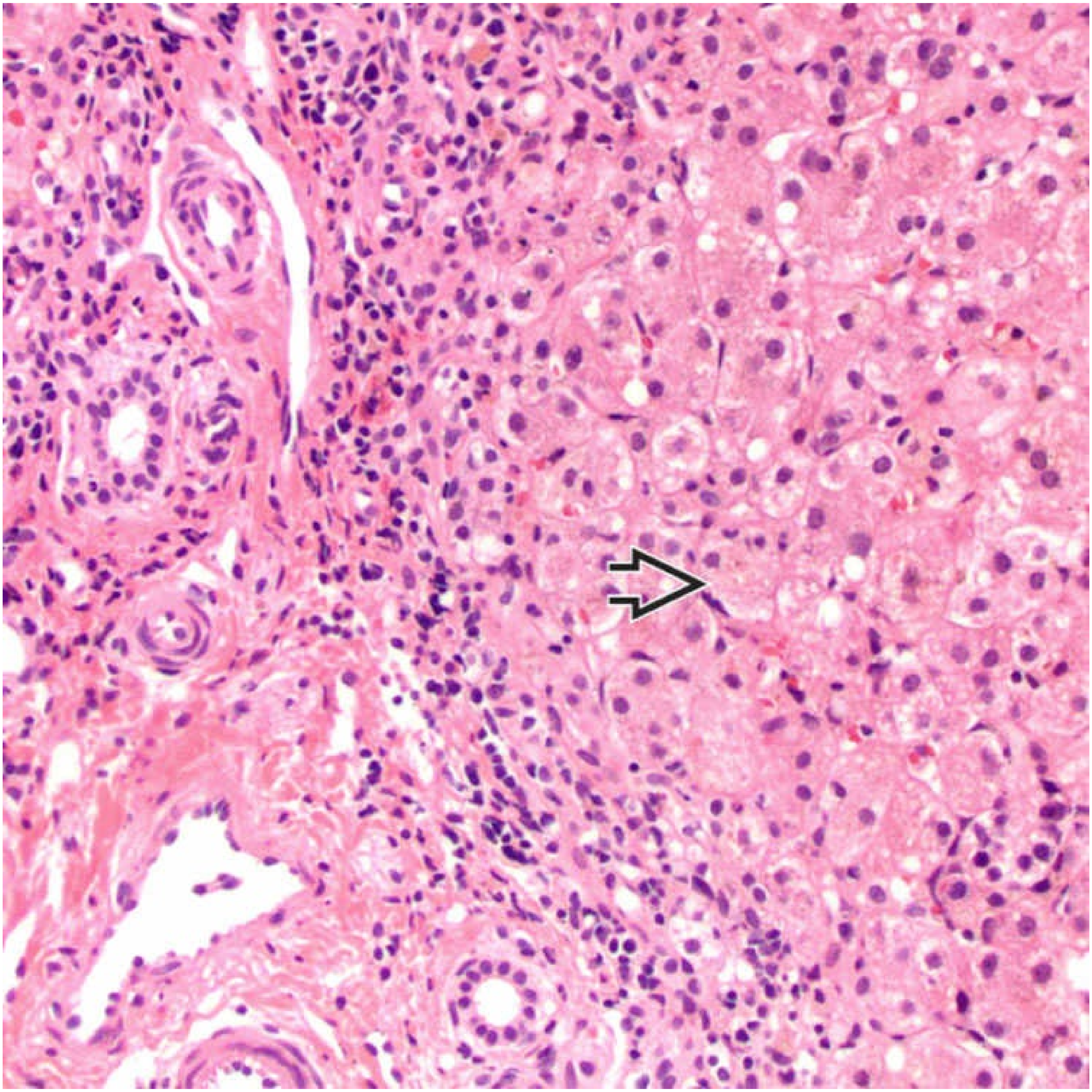
- BRIC is characterized by cholestasis during attacks but no histologic progression
- PFIC is characterized by increasing fibrosis and may show duct paucity, giant cell hepatitis, or bile ductules with bile plugging, depending on subtype
- Neonatal cholestatic disorder with normal GGT and elevated serum bile acids suggests PFIC1 or PFIC2, whereas elevated GGT suggests possibility of PFIC3

Pathologic Interpretation Pearls

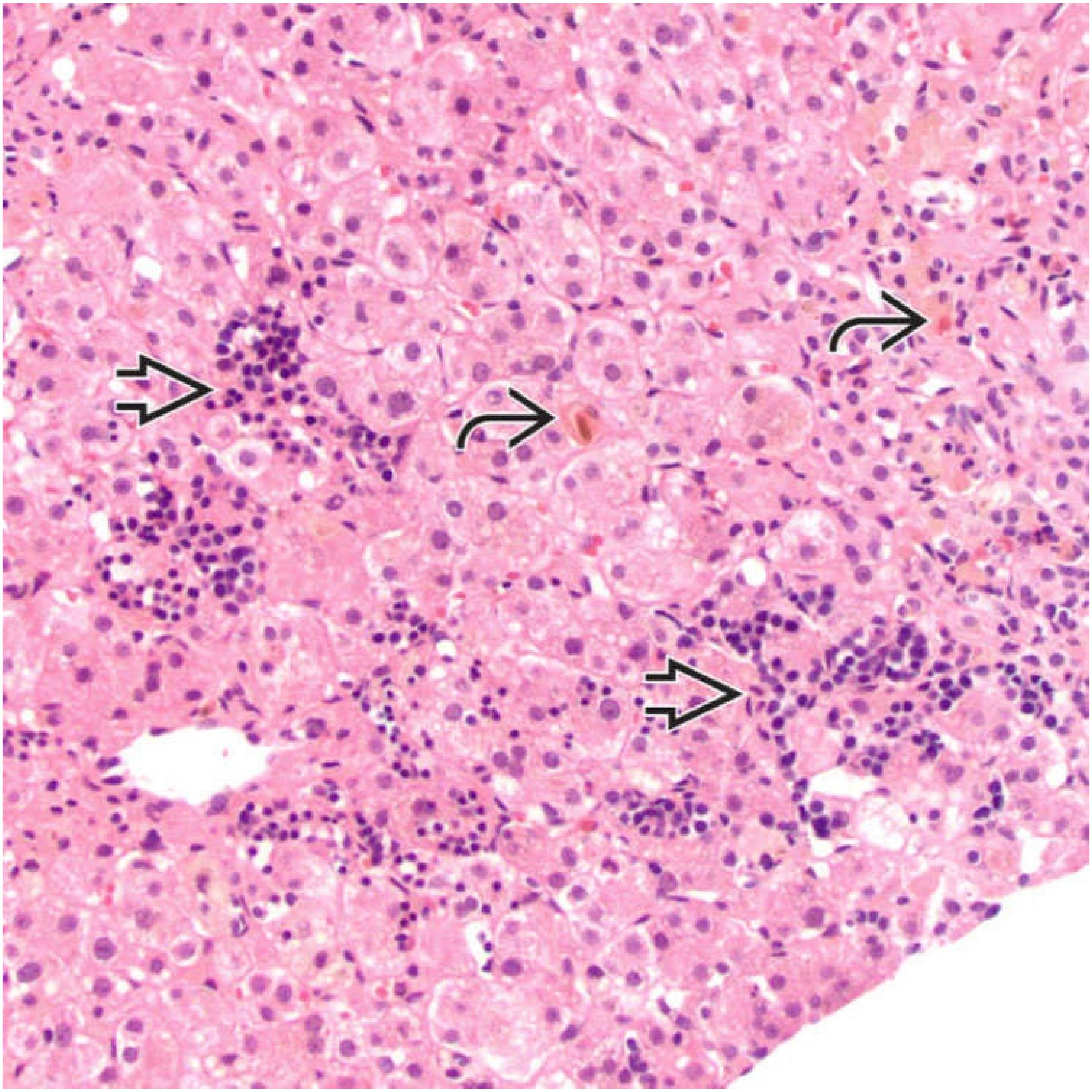
- PFIC1 shows bland cholestasis, PFIC2 shows pattern of giant cell hepatitis, and PFIC3 shows duct proliferation with bile plugs



Nodule Formation
Biopsy in an infant with PFIC2 (BSEP deficiency) shows nodule formation and portal inflammation.

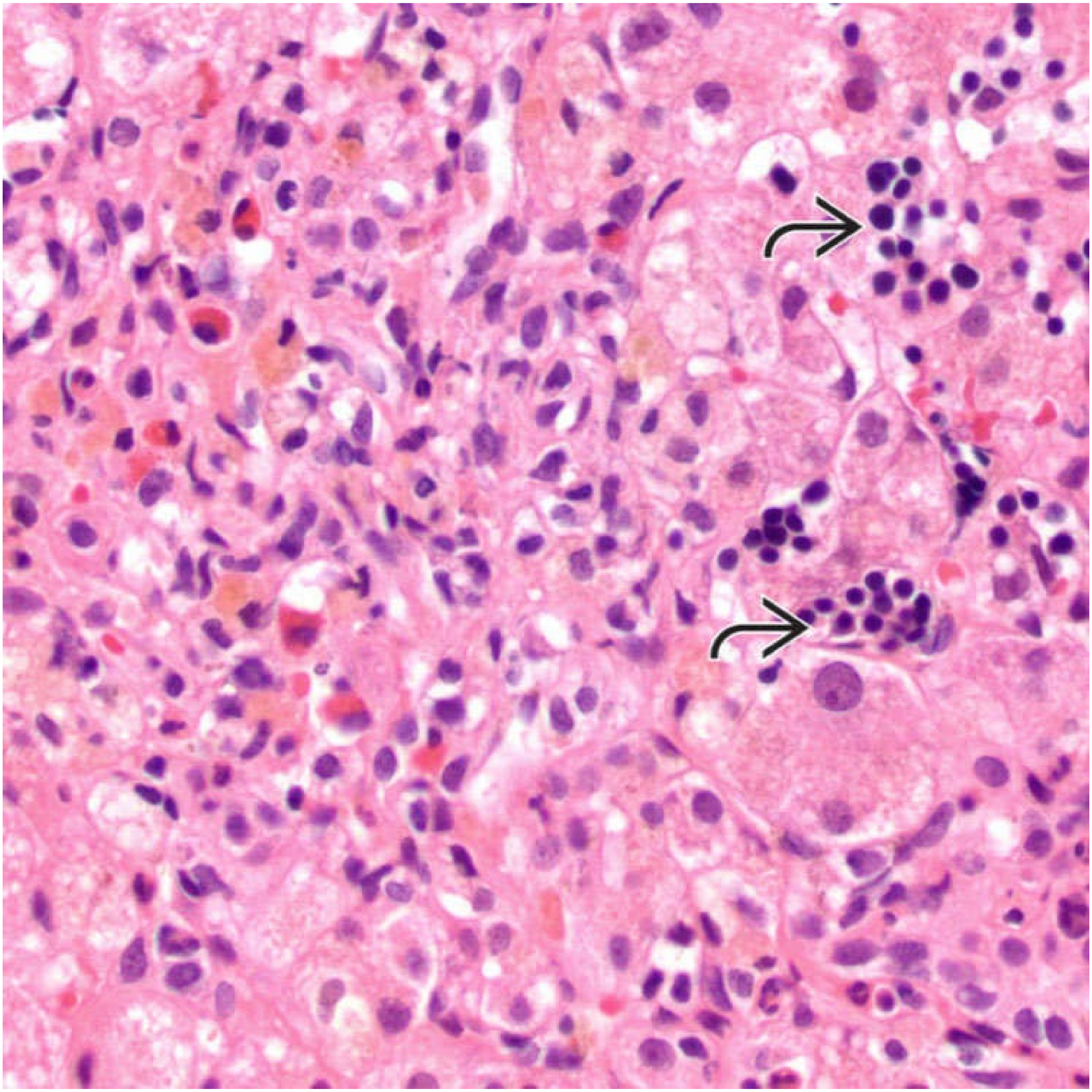


Mild Inflammation
Higher magnification of a biopsy in an infant with PFIC2 shows perinodular inflammation and bile pigment within hepatocytes ➪ .

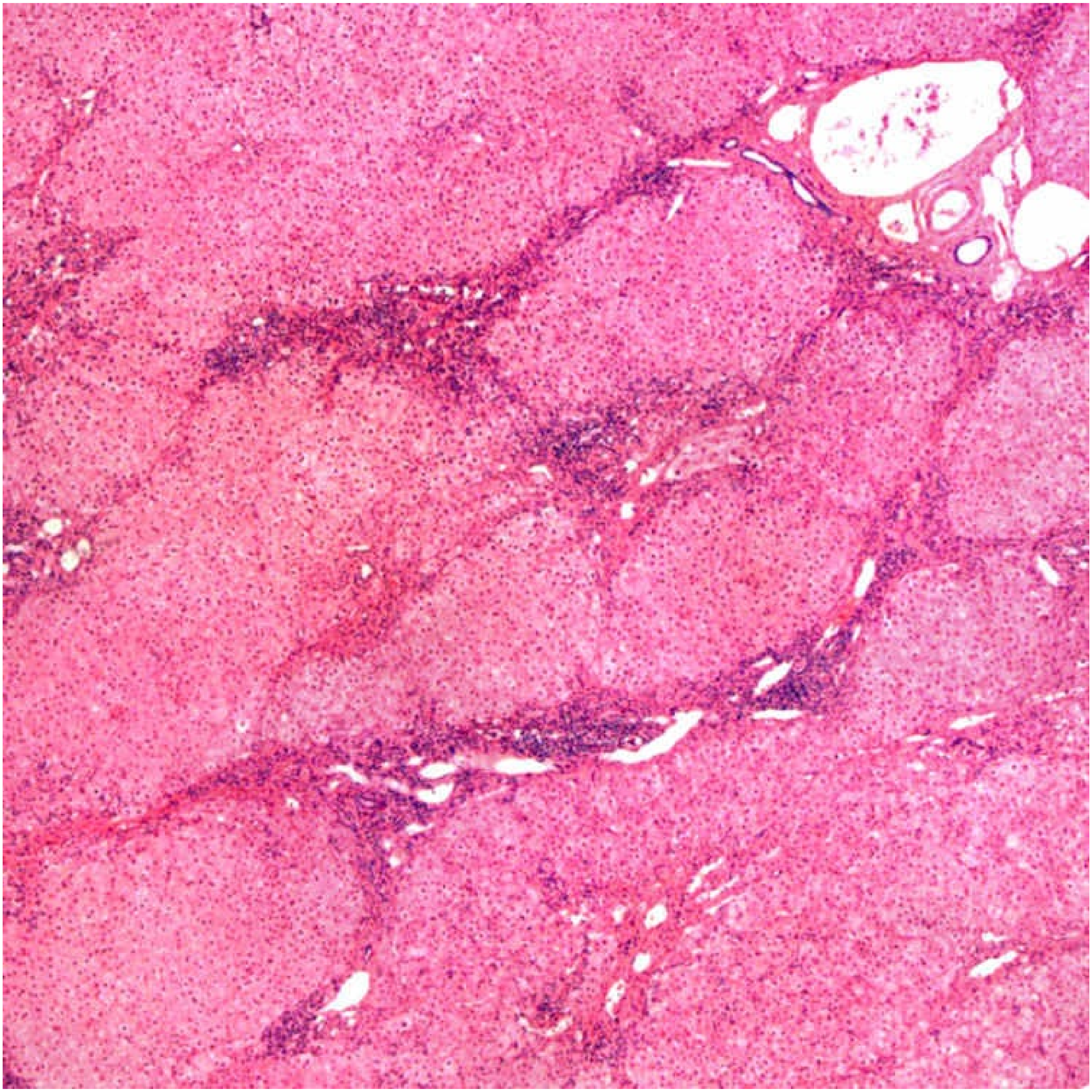


Bile Plugs

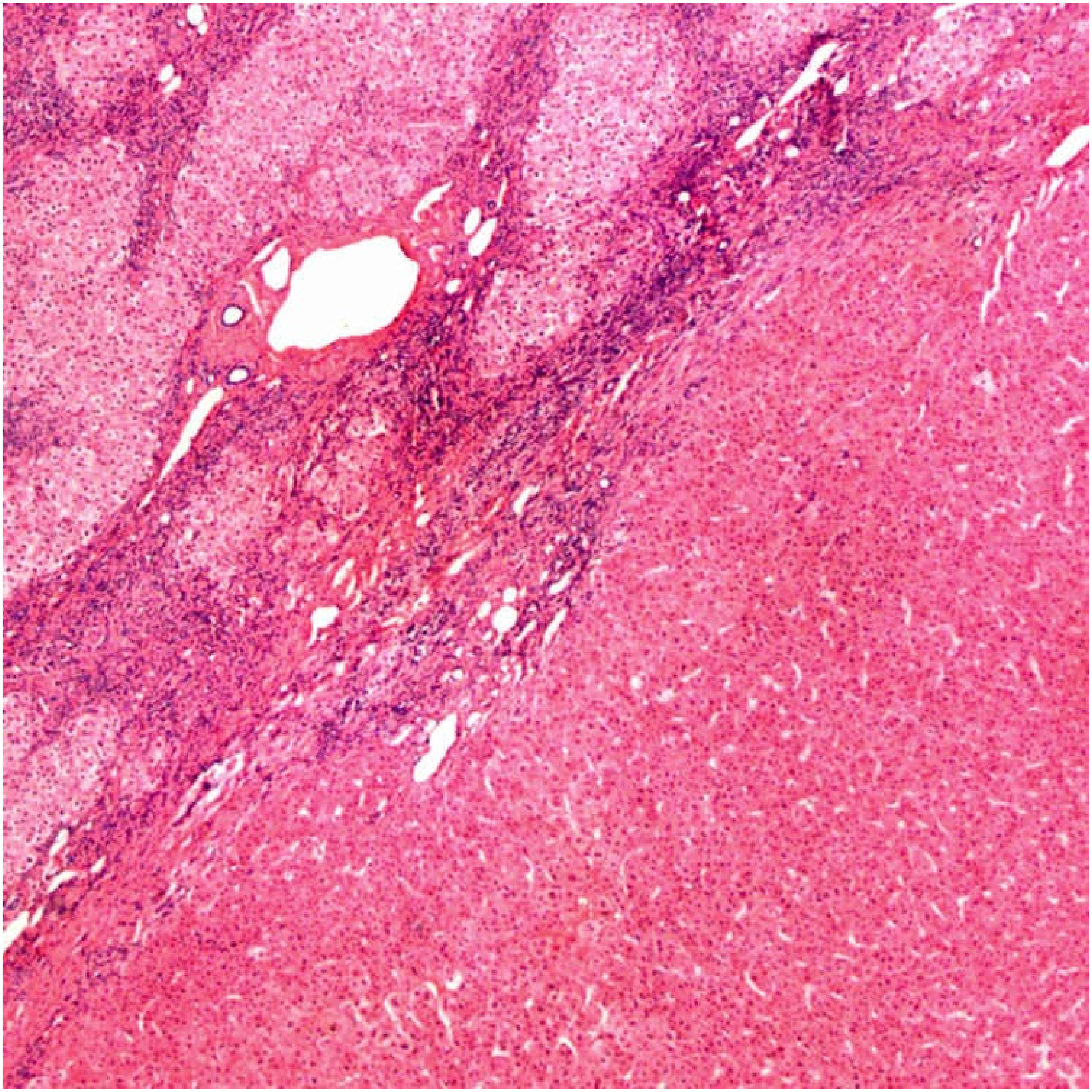
Biopsy in an infant with PFIC2 shows bile plugs within canaliculi, inflammation, and extramedullary hematopoiesis .



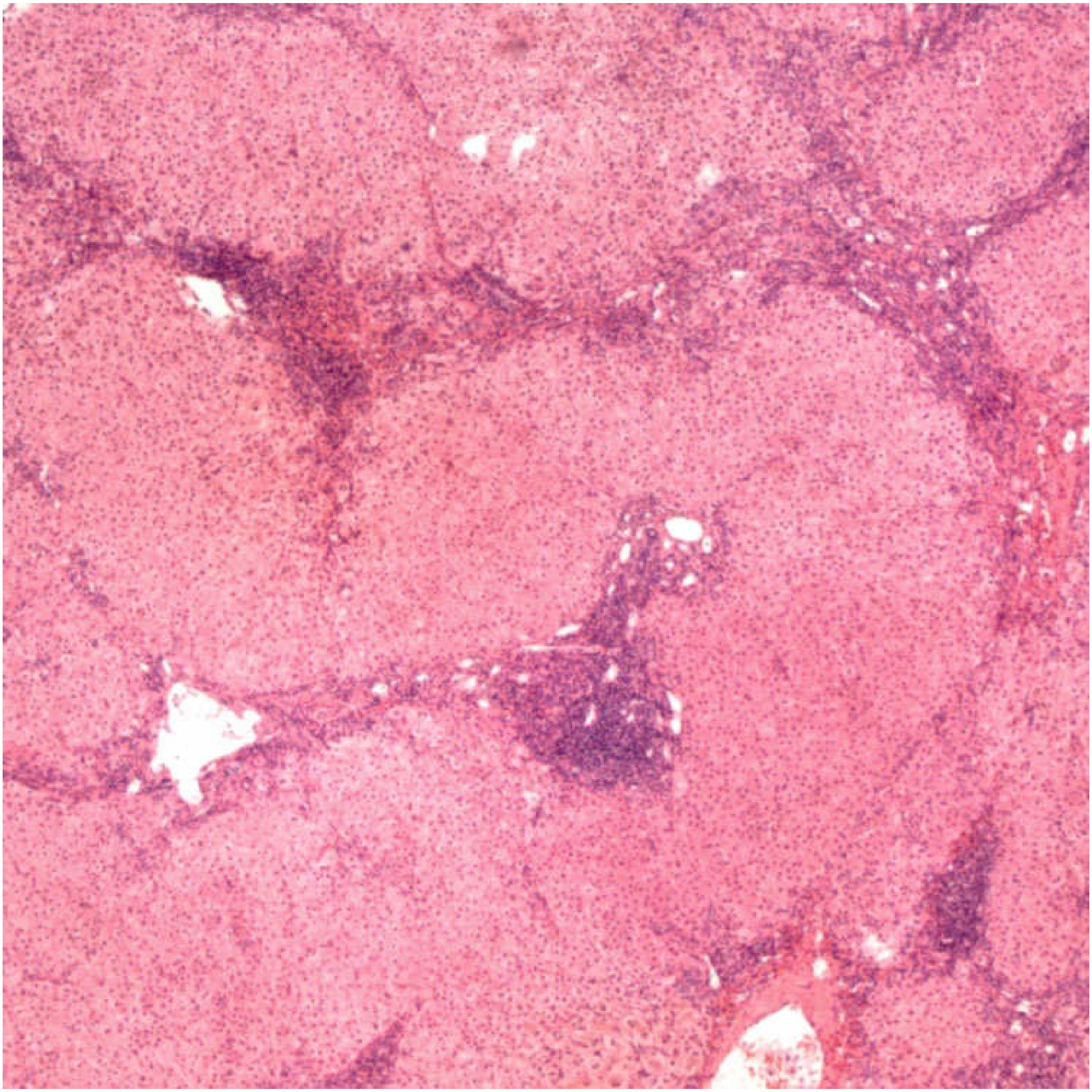
Extramedullary Hematopoiesis
High magnification of a biopsy in an infant with PFIC2 shows bile pigment in the liver, mixed inflammatory infiltrates (left), and extramedullary hematopoiesis ↱ .



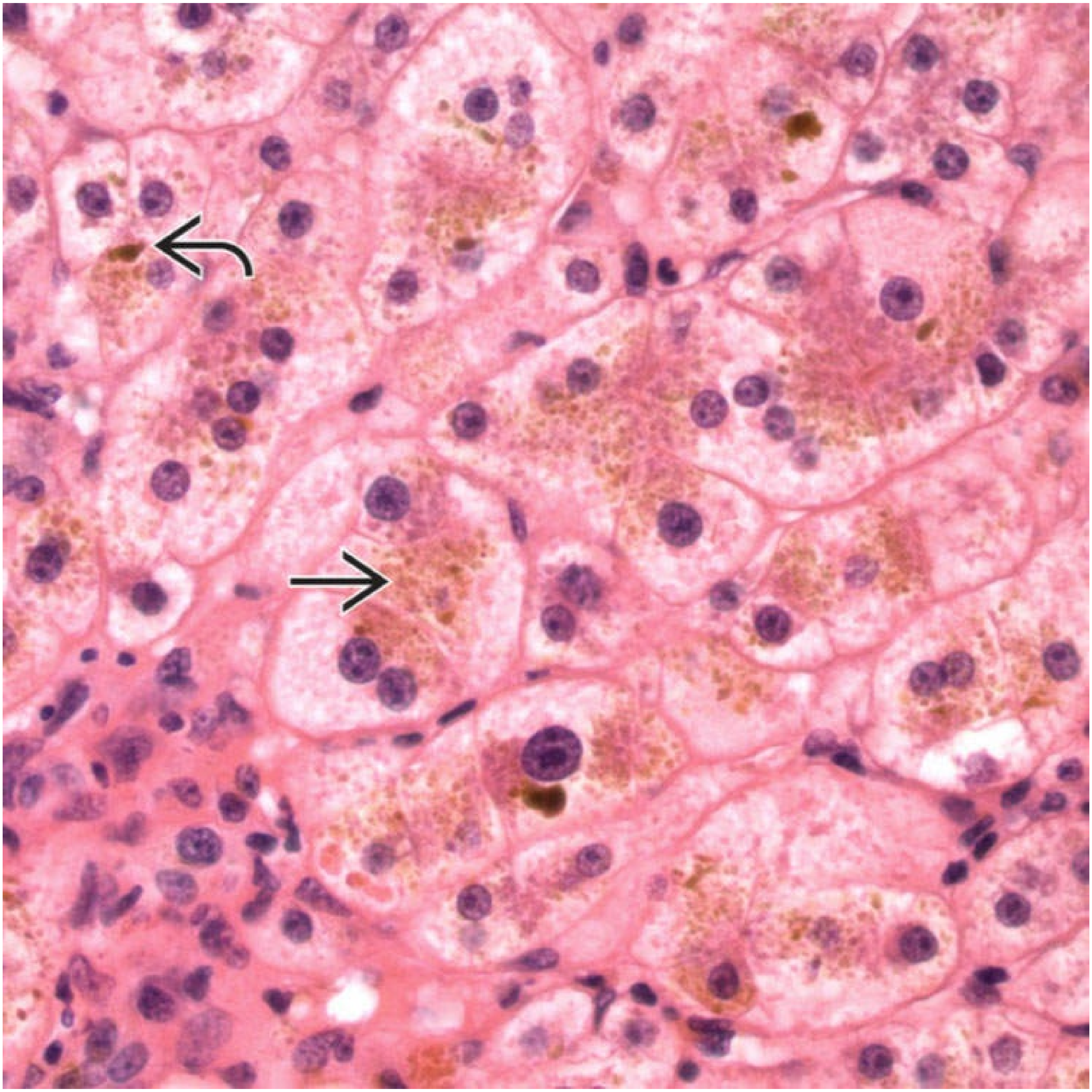
Micronodular Cirrhosis
Low-power view of an explanted liver in a child with PFIC2 shows micronodular cirrhosis and septal inflammation.



Bland Hepatocytes
Hepatocytic neoplasm (lower right) in an explanted liver of a child with PFIC2 is shown. The tumor is composed of bland hepatocytes. Although PFIC2 is associated with the development of hepatocellular carcinoma, the tumor in this case was interpreted as a hepatic adenoma.

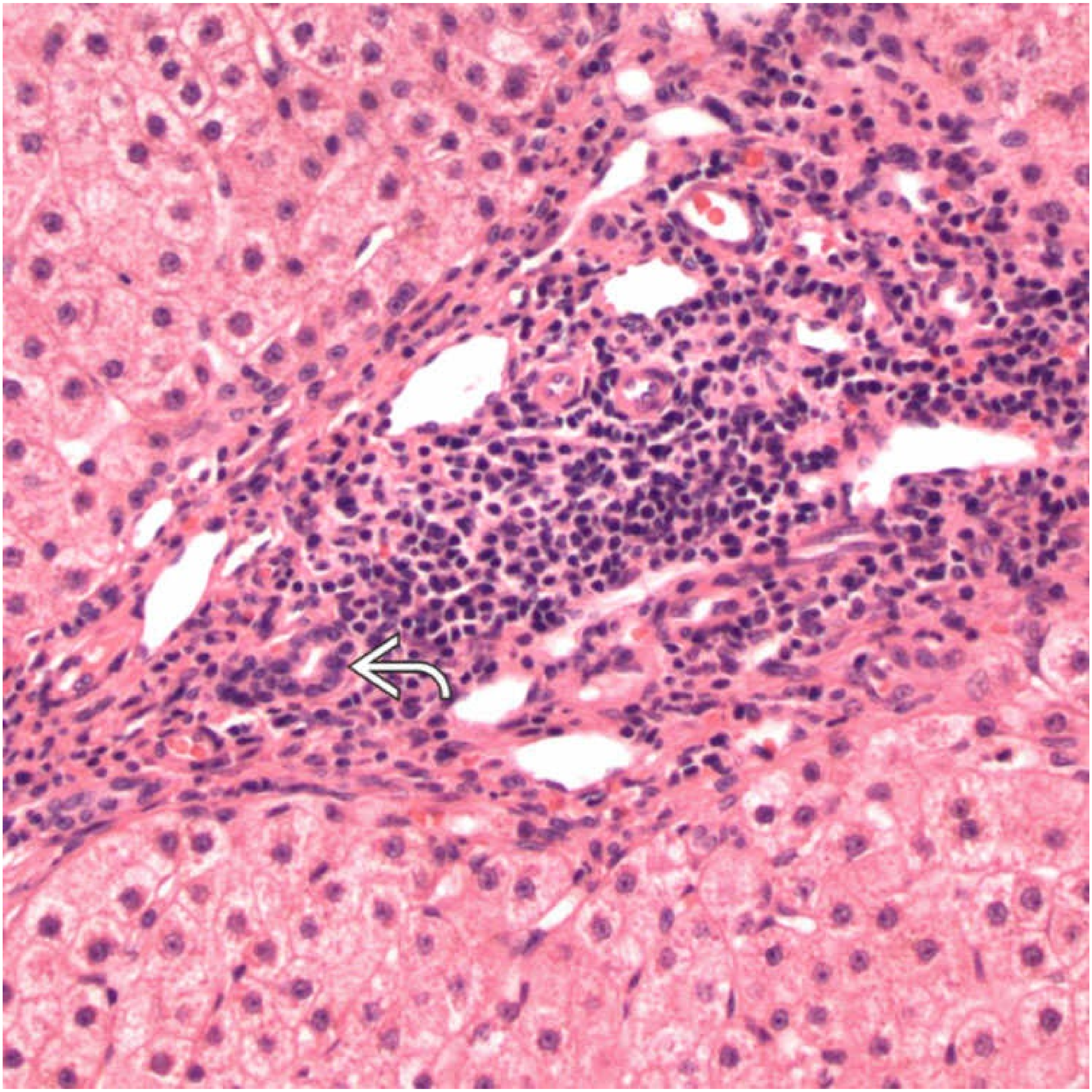


Biliary Pattern
H&E-stained section of liver explant in PFIC2 shows biliary pattern of fibrosis with portal-portal bridging and inflammation in septa.



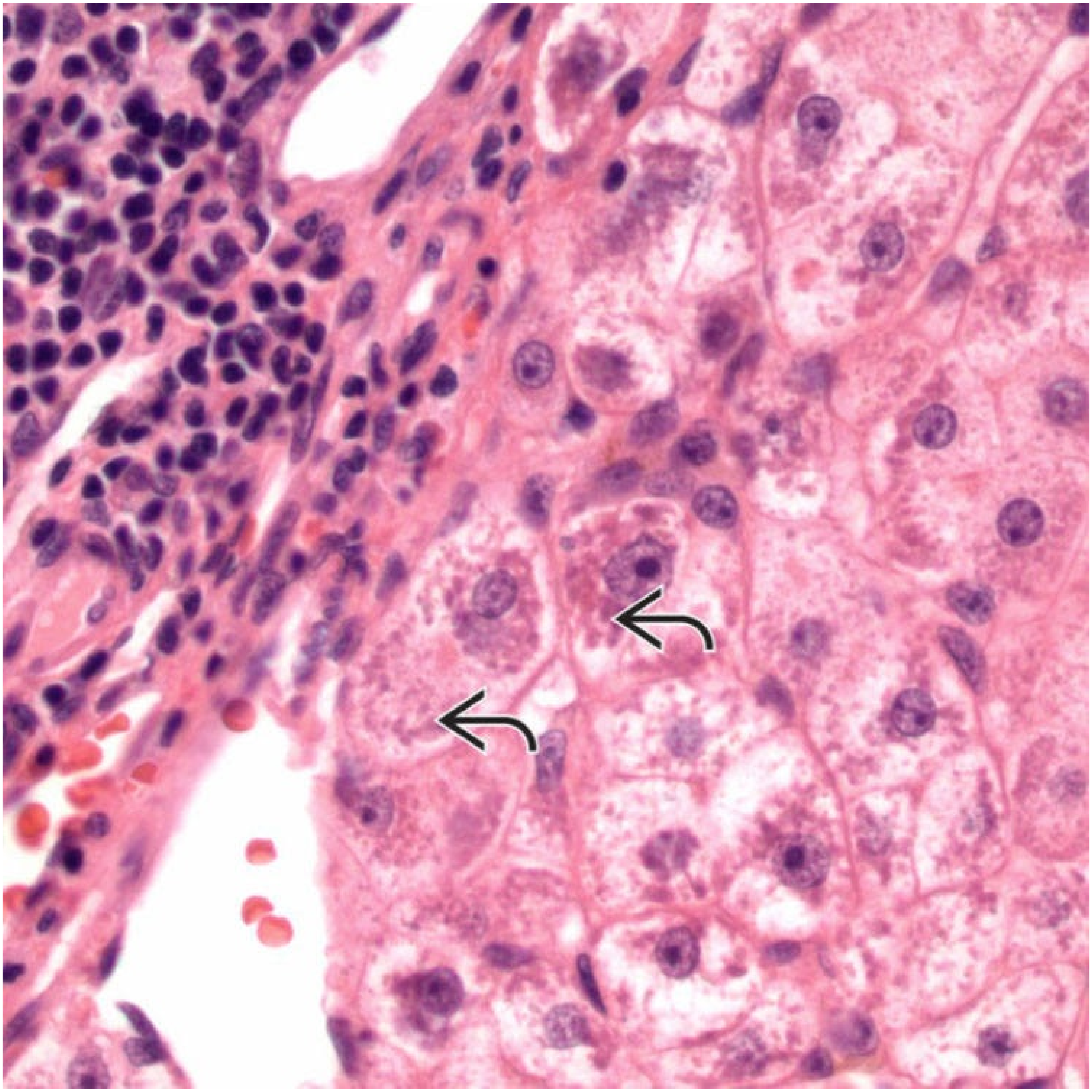
Rosetting Architecture

H&E-stained section of liver explant in PFIC2 shows pigment in hepatocytes → and canaliculi ↷, consistent with bile. The hepatocytes show rosetting architecture.

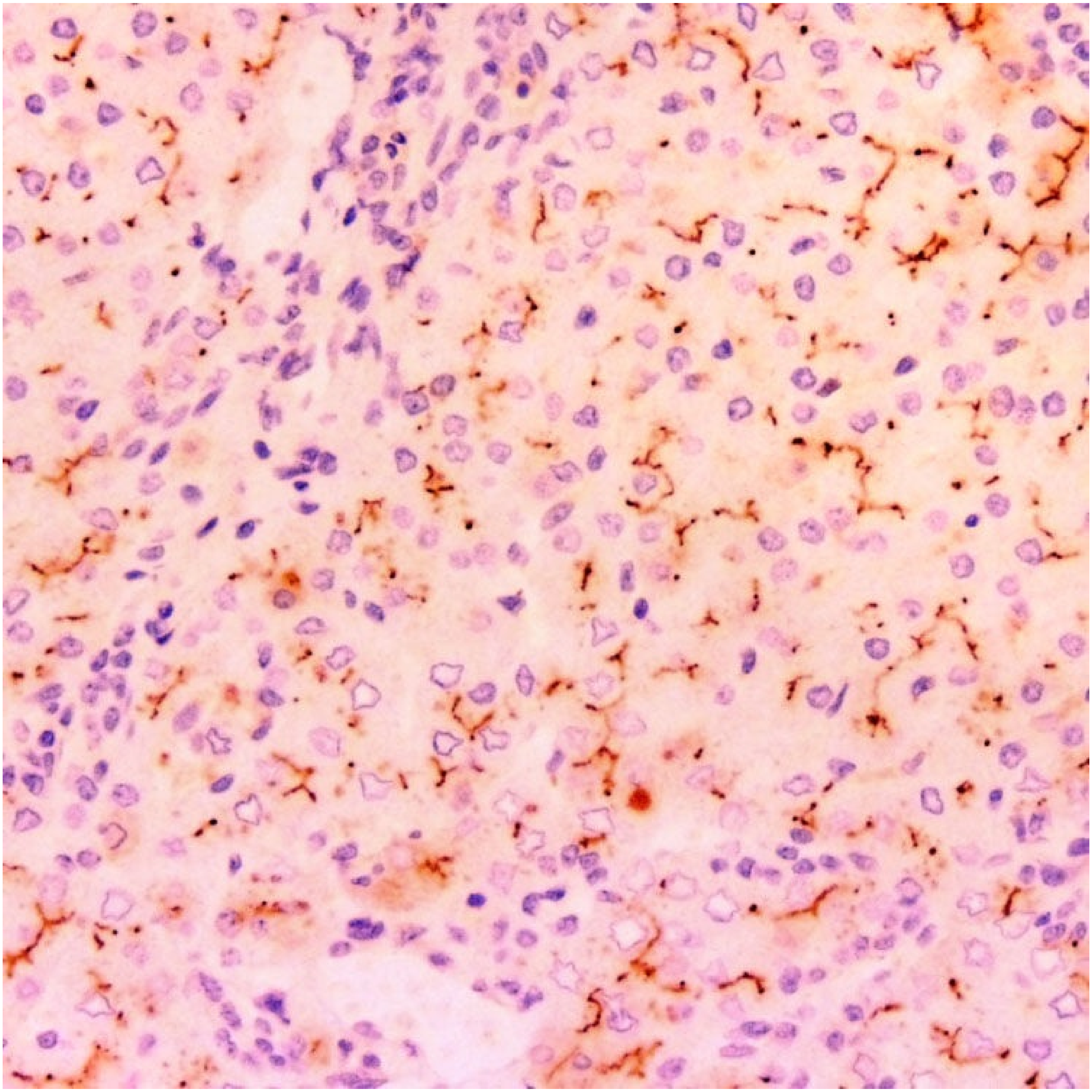


Mononuclear Infiltrates

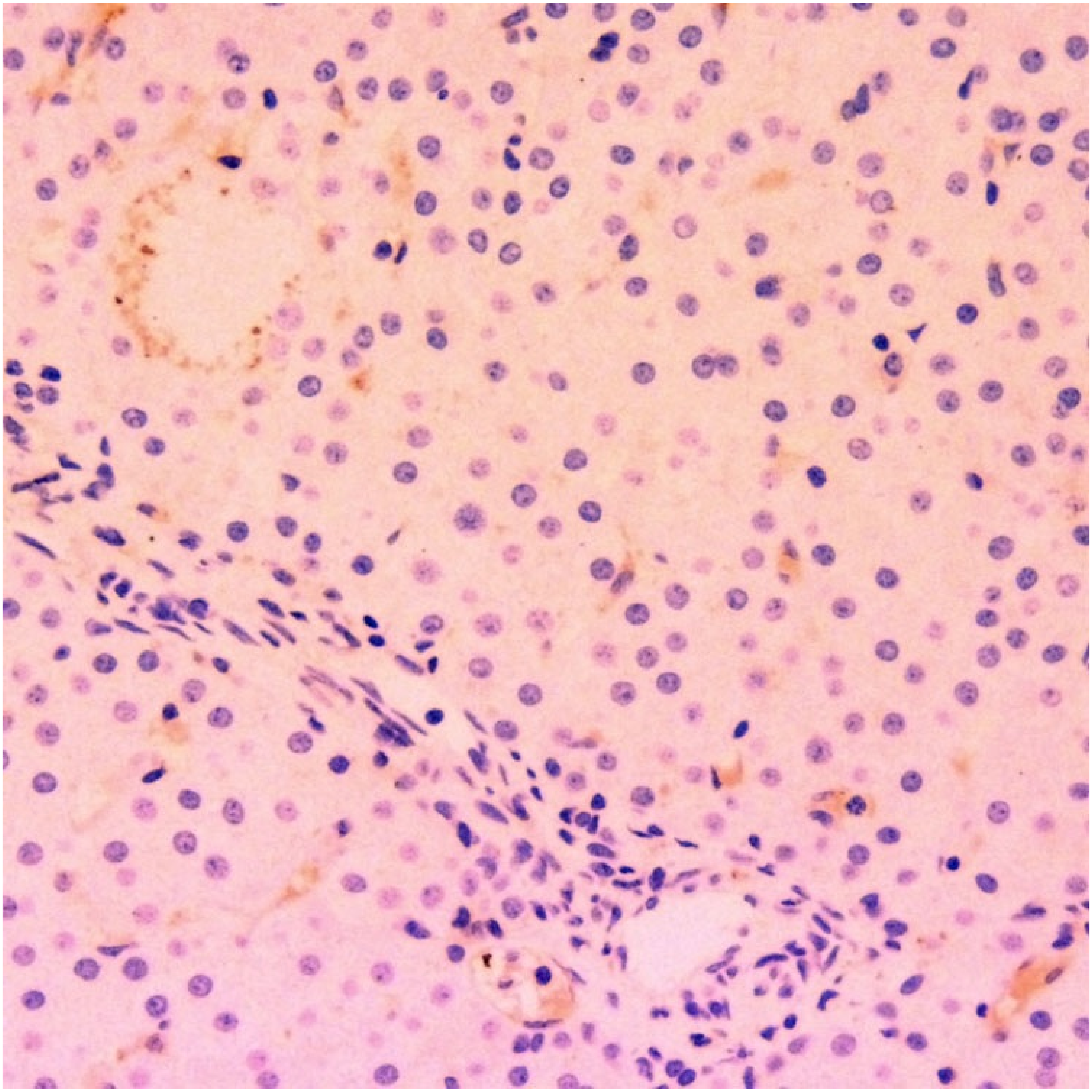
H&E-stained section of a portal tract in PFIC2 shows mononuclear infiltrates. A small duct is visible .



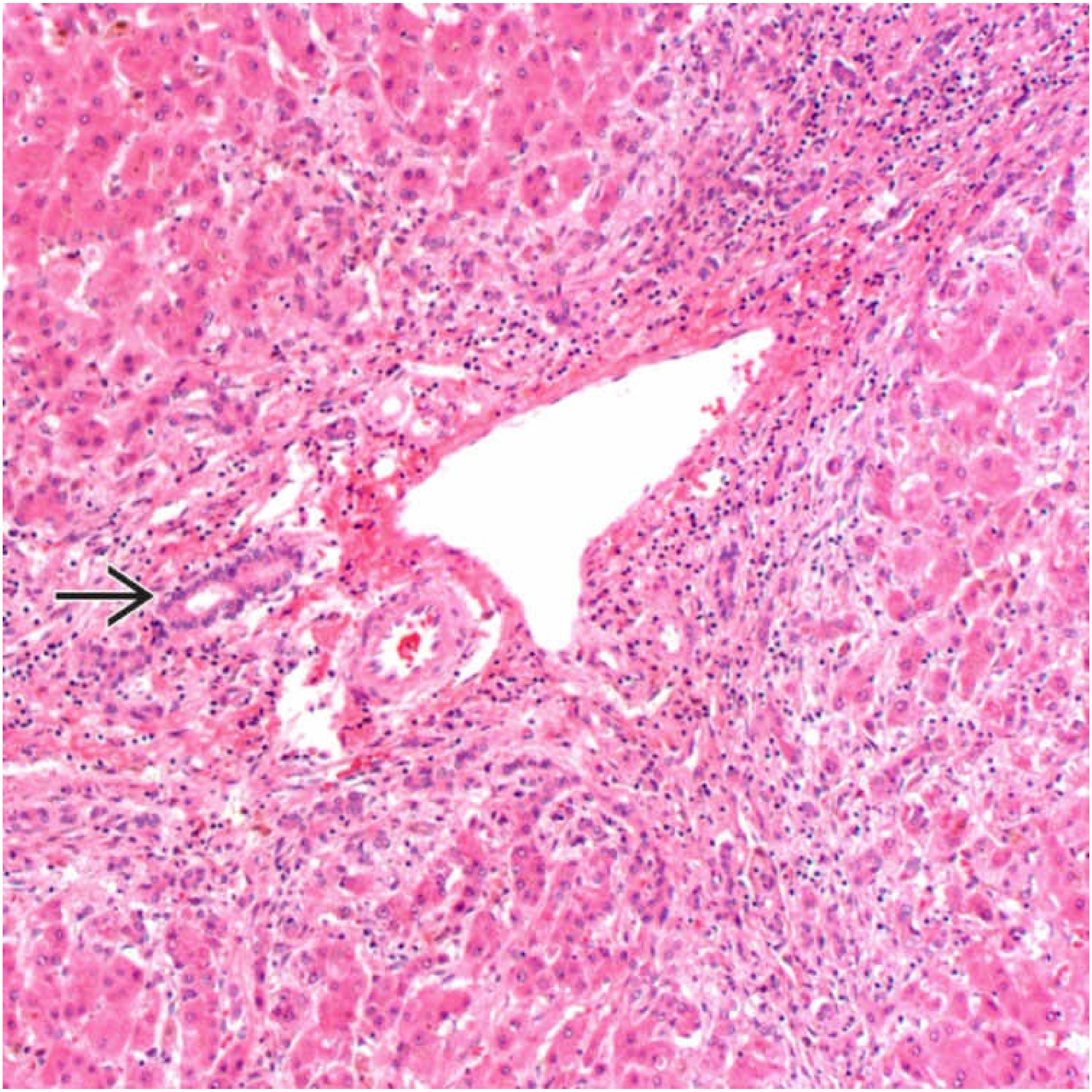
Mallory-Denk Bodies
H&E-stained section of an explant in PFIC2 shows changes of chronic cholestasis with periportal swelling of hepatocytes and Mallory-Denk bodies.



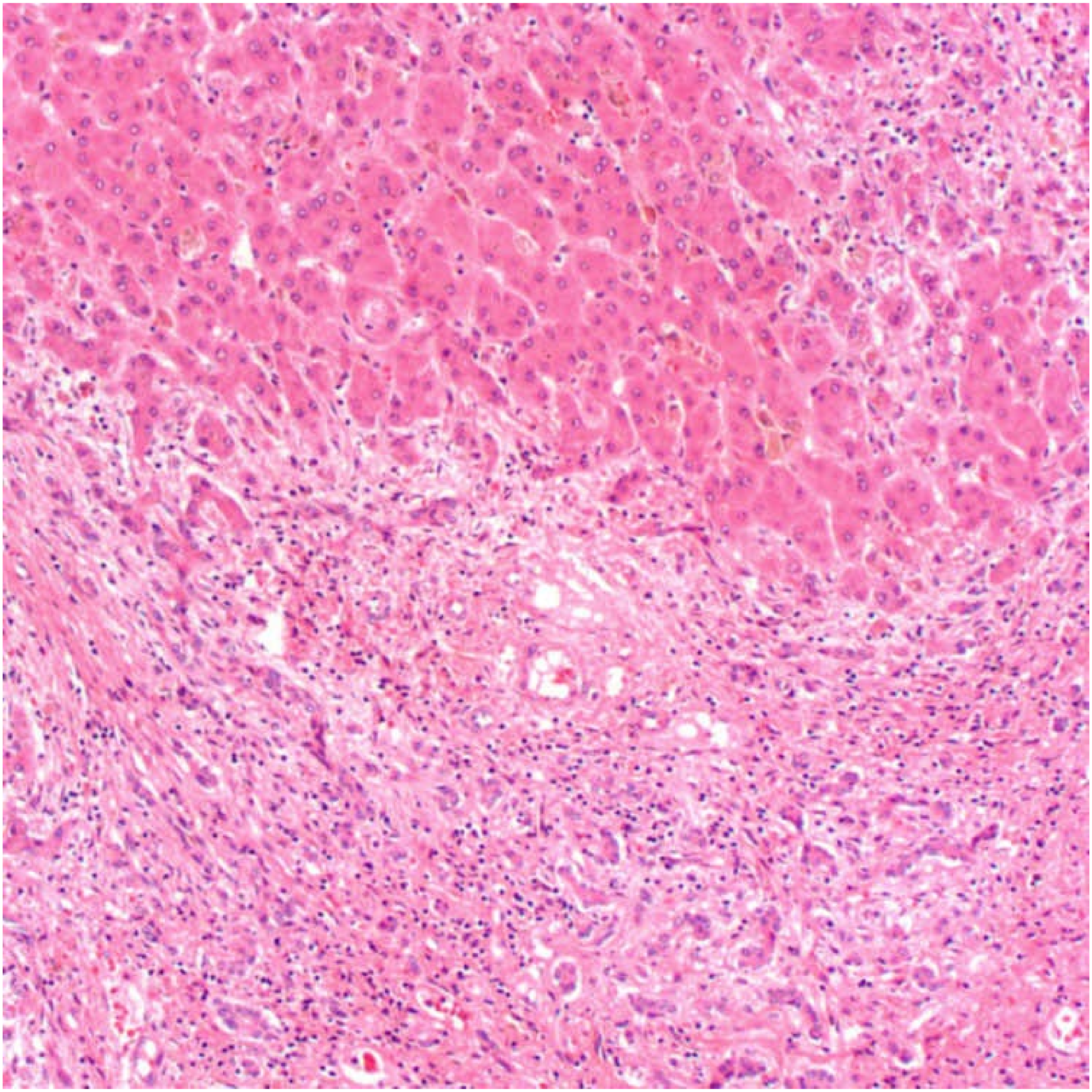
BSEP Stain
Immunohistochemical stain for BSEP in control tissue shows canalicular staining (red-brown).



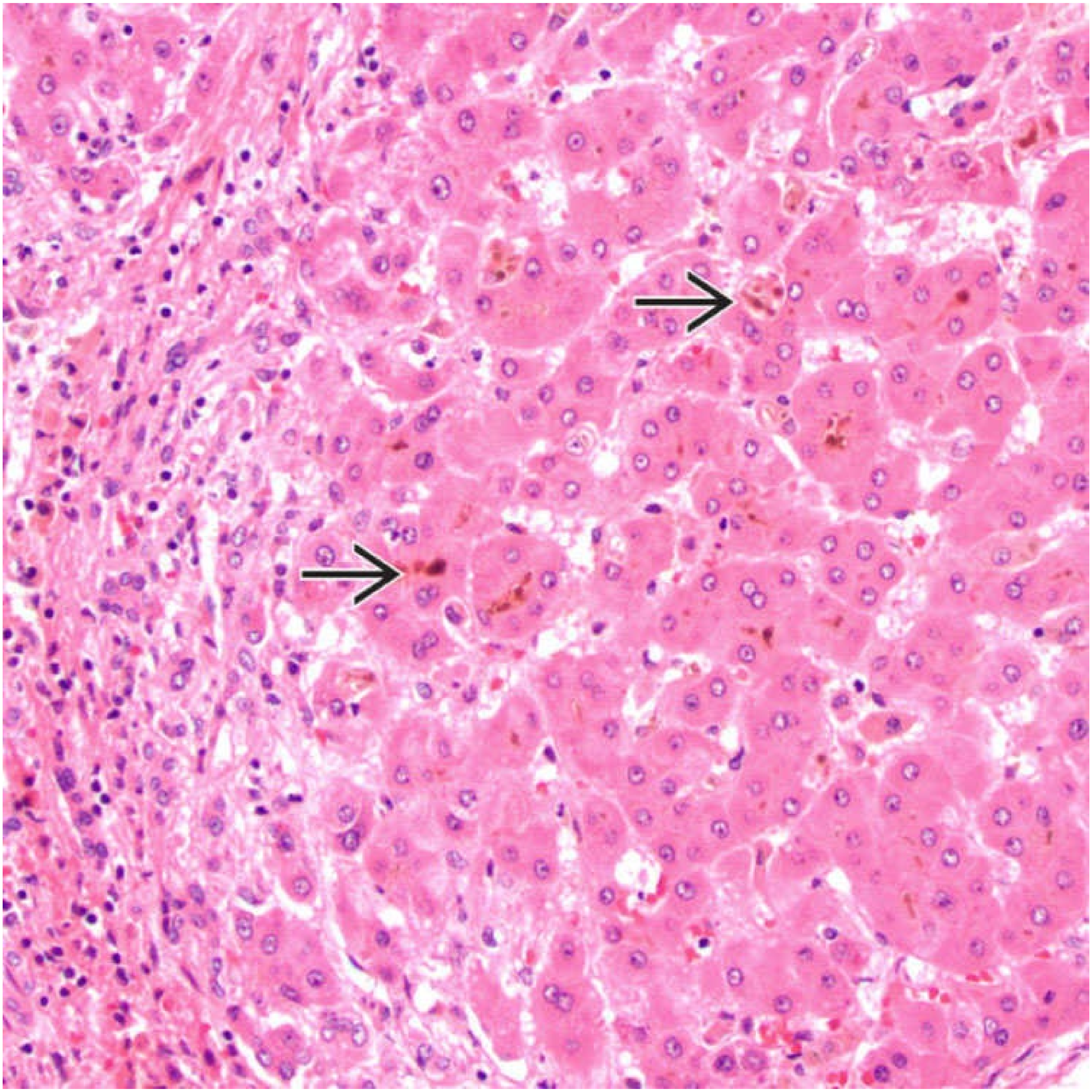
BSEP Stain
Immunohistochemical stain for BSEP in a patient explant shows absence of canalicular expression of the bile salt transporter.



Fibrous Expansion
Portal tract in cirrhosis secondary to PFIC1 shows fibrous expansion with bile ductular reaction at the periphery of the septa and pallor at the edge of the nodules, typical of biliary cirrhosis. An interlobular bile duct is present →.

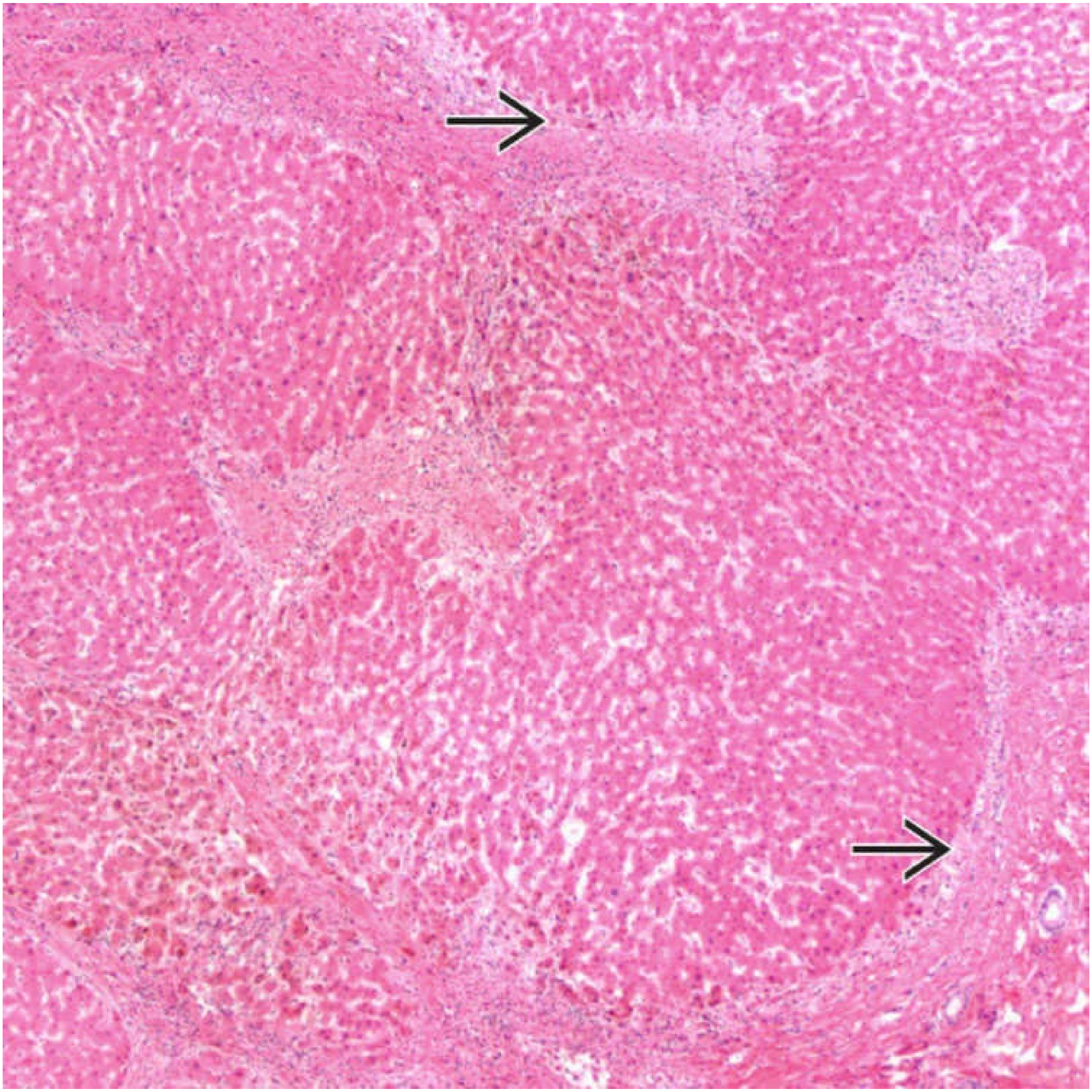


Ductular Reaction
H&E-stained section of cirrhosis secondary to PFIC1 shows ductular reaction and inflammation in the septa.

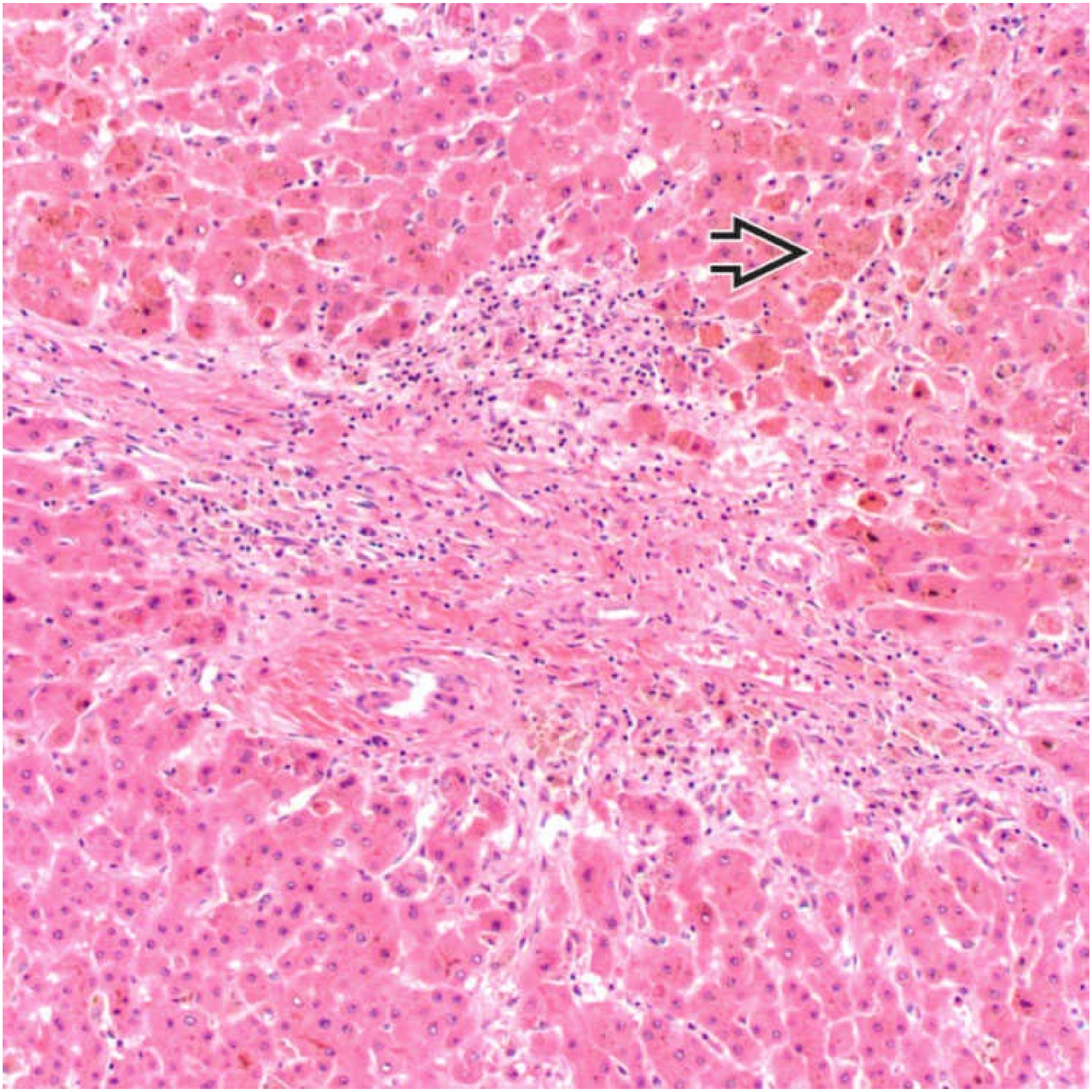


Bile Stasis

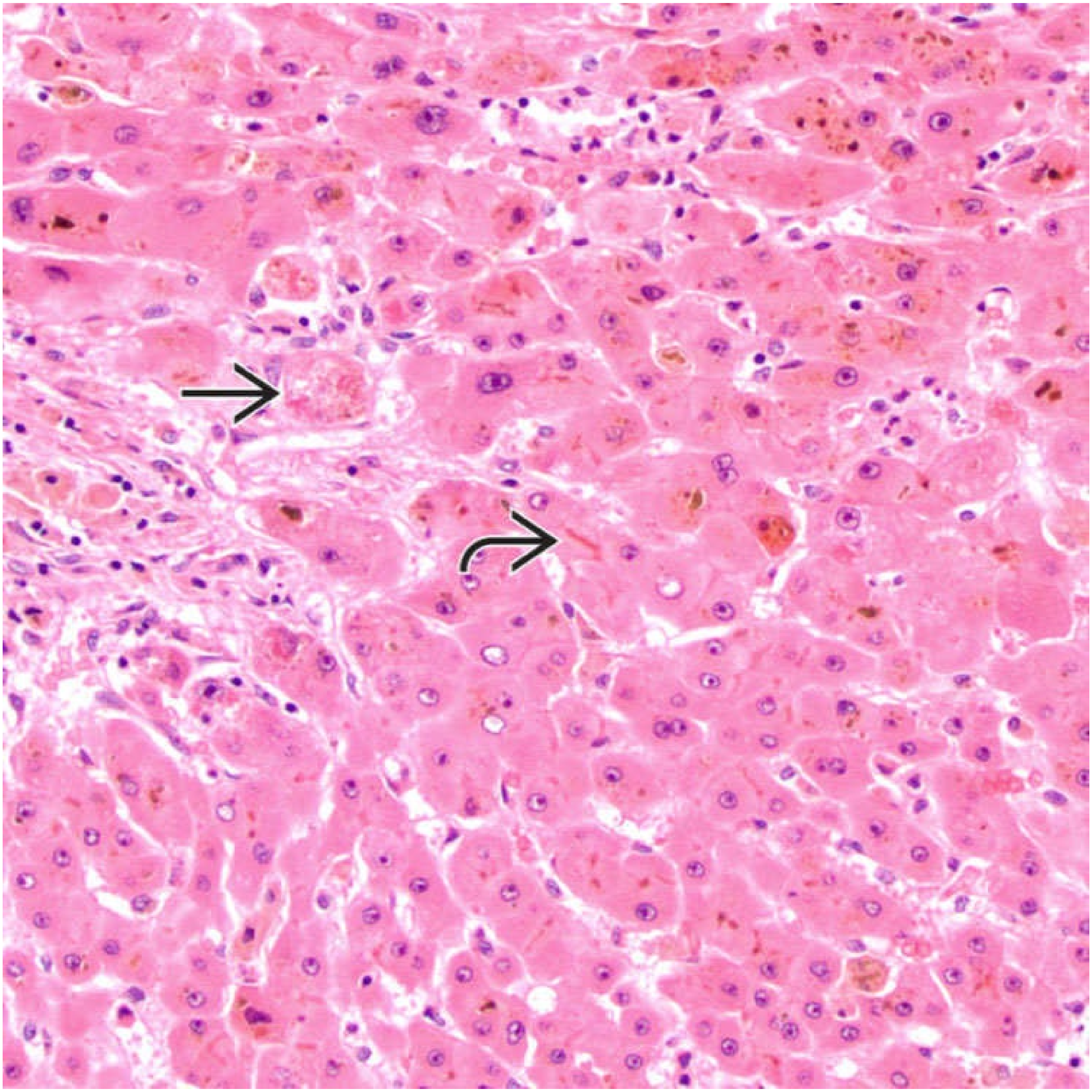
H&E-stained section of cirrhosis secondary to PFIC1 shows bile stasis in canaliculi → and pallor at the edge of the nodule, typical of biliary cirrhosis.



Biliary Cirrhosis
Low-power view of biliary cirrhosis in PFIC3 shows irregular islands of hepatic parenchyma dissected by fibrous bridges. Note the pallor at the edges of the nodule →, typical of biliary cirrhosis.



Periseptal Hepatocytes
H&E-stained section of a portal tract in cirrhosis secondary to PFIC3 shows absent bile duct. There is bile stasis manifested as pigment in periseptal hepatocytes .



Mallory Hyaline

High-power view of PFIC3 shows marked bile stasis within canaliculi as well as Mallory-Denk bodies at the edges of the nodules . Mallory hyaline is a frequent finding in chronic cholestatic disorders.

SELECTED REFERENCES

1. El-Guindi, MA, et al. Hepatic immunohistochemistry of bile transporters in progressive familial intrahepatic cholestasis. *Ann Hepatol*. 2016; 15(2):222–229.
2. Evason, K, et al. Morphologic findings in progressive familial intrahepatic cholestasis 2 (PFIC2): correlation with genetic and immunohistochemical studies. *Am J Surg Pathol*. 2011; 35(5):687–696.
3. Morotti, RA, et al. Progressive familial intrahepatic cholestasis (PFIC) type 1, 2, and 3: a review of the liver pathology findings. *Semin Liver Dis*. 2011; 31(1):3–10.

4. Cai, SY, et al. ATP8B1 deficiency disrupts the bile canalicular membrane bilayer structure in hepatocytes, but FXR expression and activity are maintained. *Gastroenterology*. 2009; 136(3):1060–1069.
5. Alissa, FT, et al. Update on progressive familial intrahepatic cholestasis. *J Pediatr Gastroenterol Nutr*. 2008; 46(3):241–252.
6. van Mil, SW, et al. Genetics of familial intrahepatic cholestasis syndromes. *J Med Genet*. 2005; 42(6):449–463.
7. Chen, F, et al. Progressive familial intrahepatic cholestasis, type 1, is associated with decreased farnesoid X receptor activity. *Gastroenterology*. 2004; 126(3):756–764.
8. Jacquemin, E. Role of multidrug resistance 3 deficiency in pediatric and adult liver disease: one gene for three diseases. *Semin Liver Dis*. 2001; 21(4):551–562.
9. Thompson, R, et al. BSEP: function and role in progressive familial intrahepatic cholestasis. *Semin Liver Dis*. 2001; 21(4):545–550.
10. van Mil, SW, et al. FIC1 disease: a spectrum of intrahepatic cholestatic disorders. *Semin Liver Dis*. 2001; 21(4):535–544.
11. Alonso, EM, et al. Histologic pathology of the liver in progressive familial intrahepatic cholestasis. *J Pediatr Gastroenterol Nutr*. 1994; 18(2):128–133.

Cystic Fibrosis, Hepatic

KEY FACTS

Terminology

- Generalized inherited disorder of exocrine gland function
  - Most common lethal autosomal recessive inherited disorder in Caucasian population
- *CFTR* mutation on chromosome 7
  - Abnormal chloride transport in apical membrane of epithelial cells

Clinical Issues

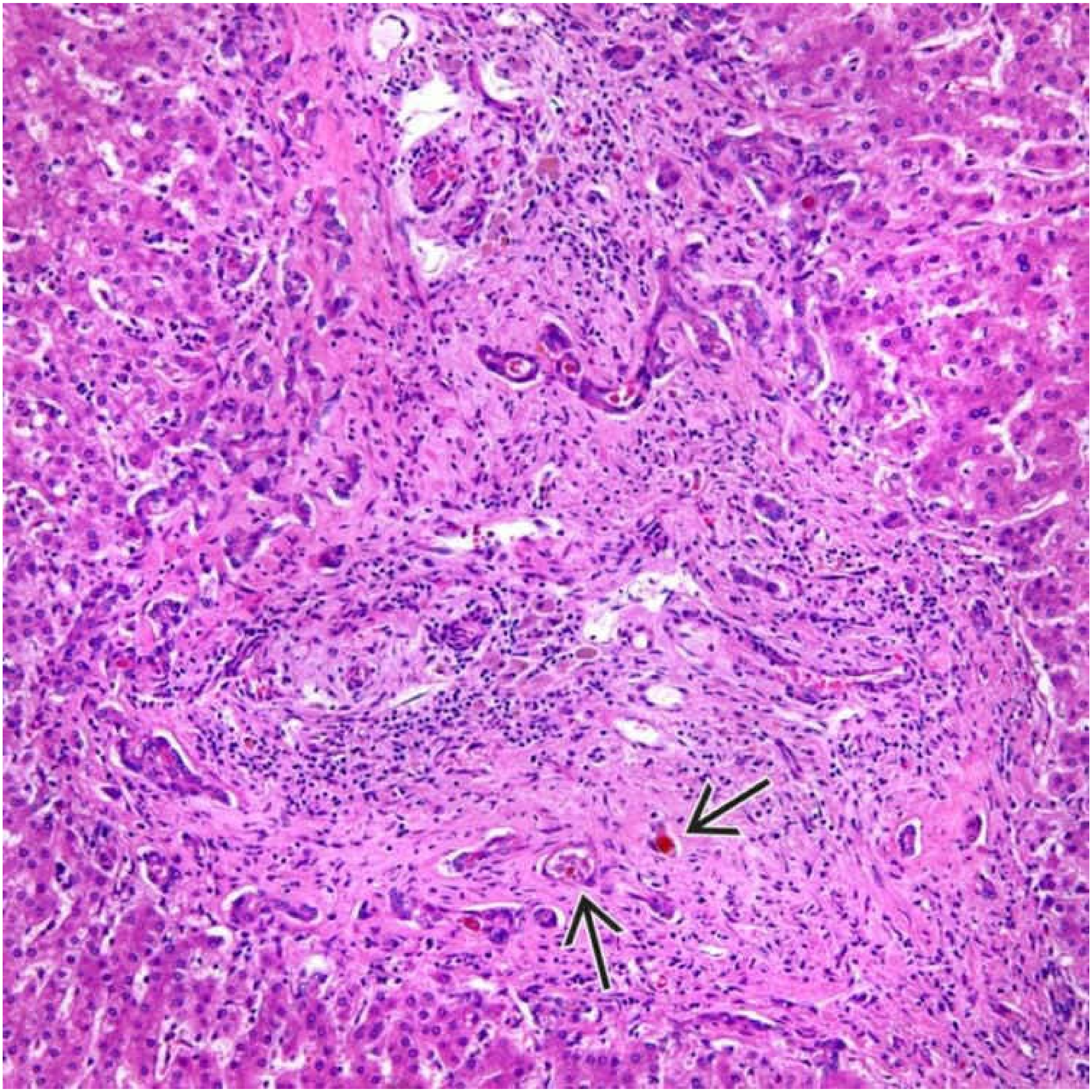
- 1 in 2,000-2,500 live births
  - Respiratory complaints are common presentation
  - Patients rarely present initially with liver disease
  - – Up to 40% of affected adolescents have evidence of liver disease
  - – Cirrhosis accounts for virtually all nonpulmonary deaths in cystic fibrosis (CF)
- As life expectancy increases, hepatobiliary disease in CF more often recognized

Microscopic

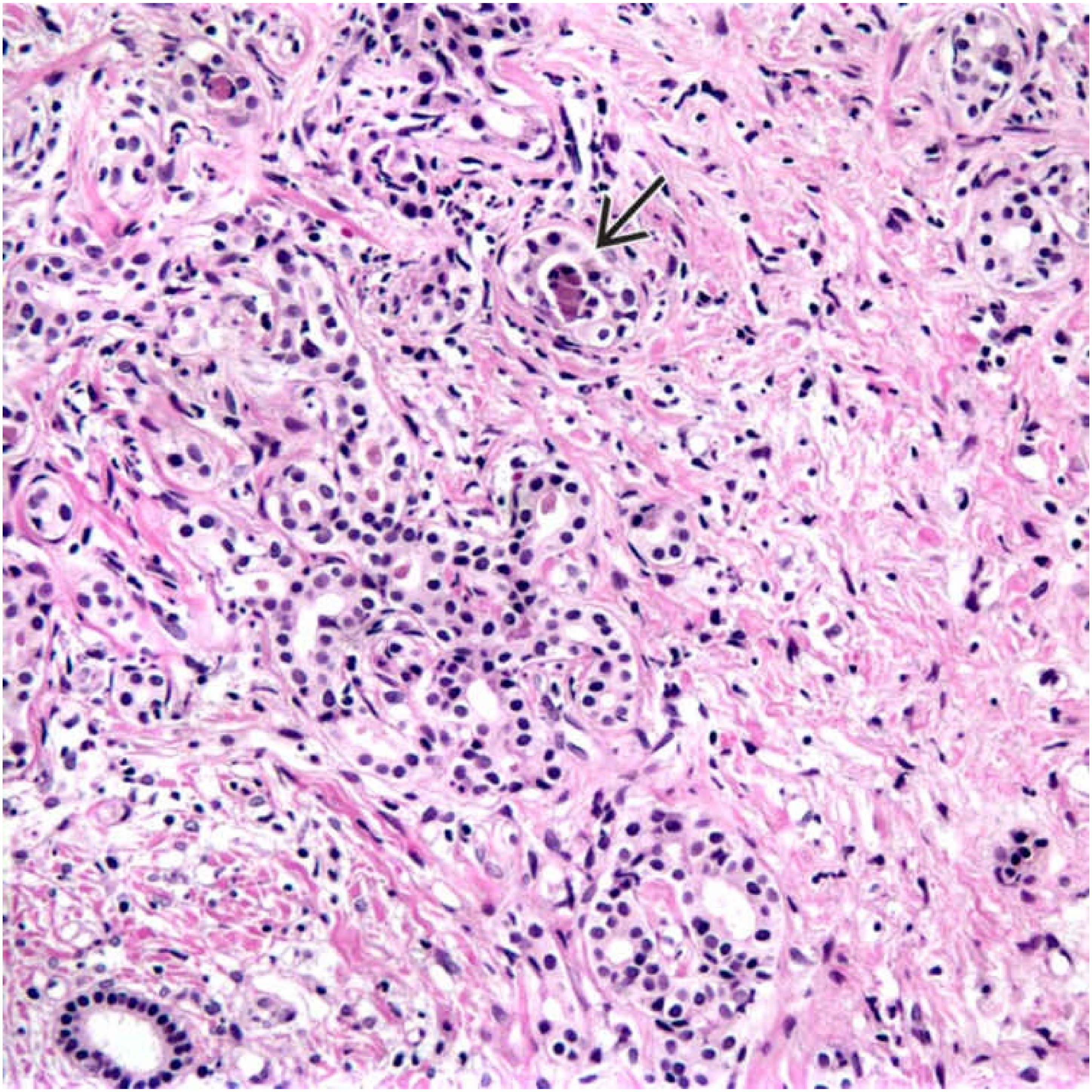
- Focal biliary fibrosis is characteristic lesion
  - Dilated, proliferated bile ductules
  - Dense secretions/concretions represent abnormal secretions of CF
  - PAS positive (diastase resistant); mucicarmine and Alcian blue negative
- Fibrous, expanded portal tracts with variable inflammation
  - Disease may progress to multilobular biliary cirrhosis

Top Differential Diagnoses

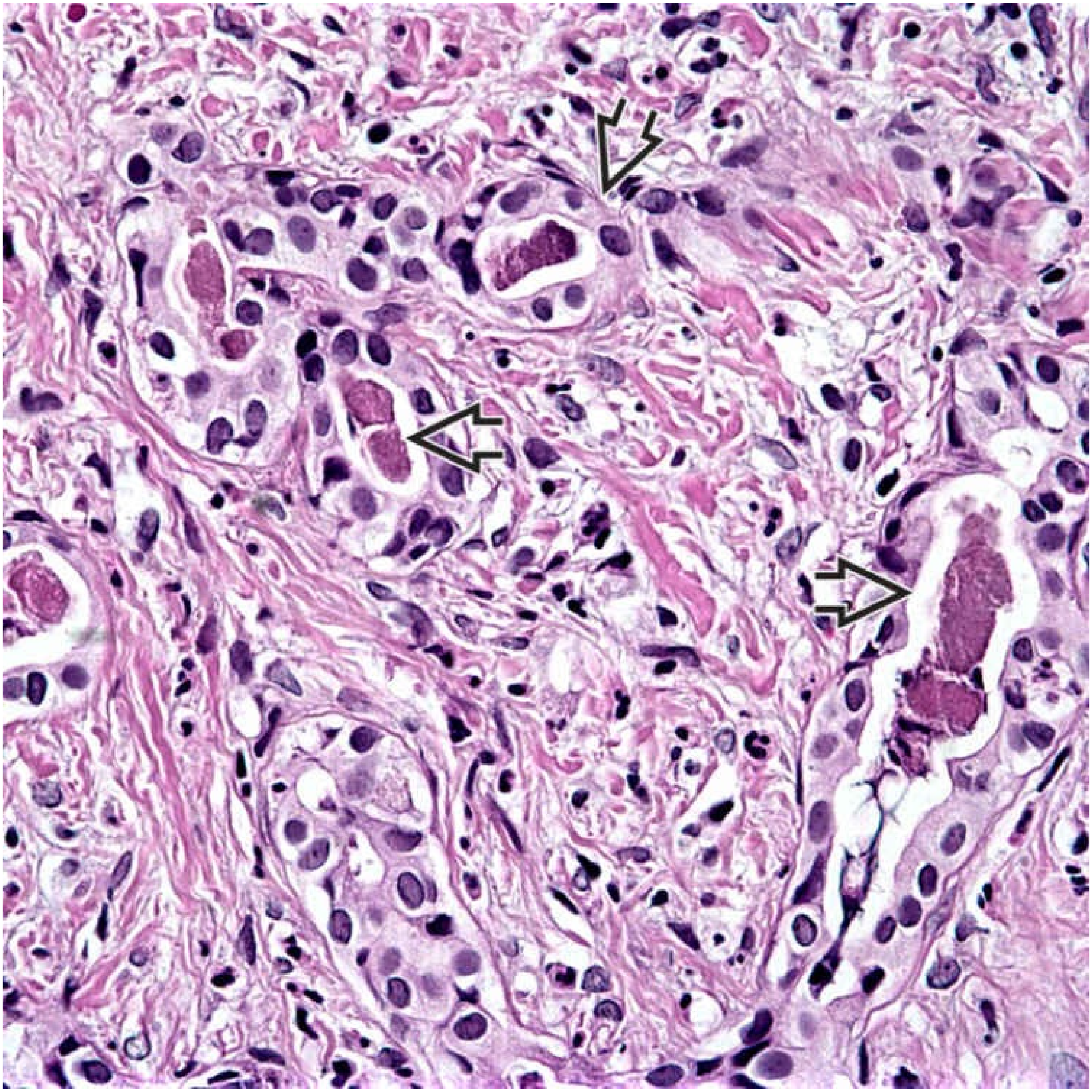
- Primary sclerosing cholangitis (PSC)
  - PSC and CF may mimic each other on ERCP
- Neonatal hepatitis of other causes



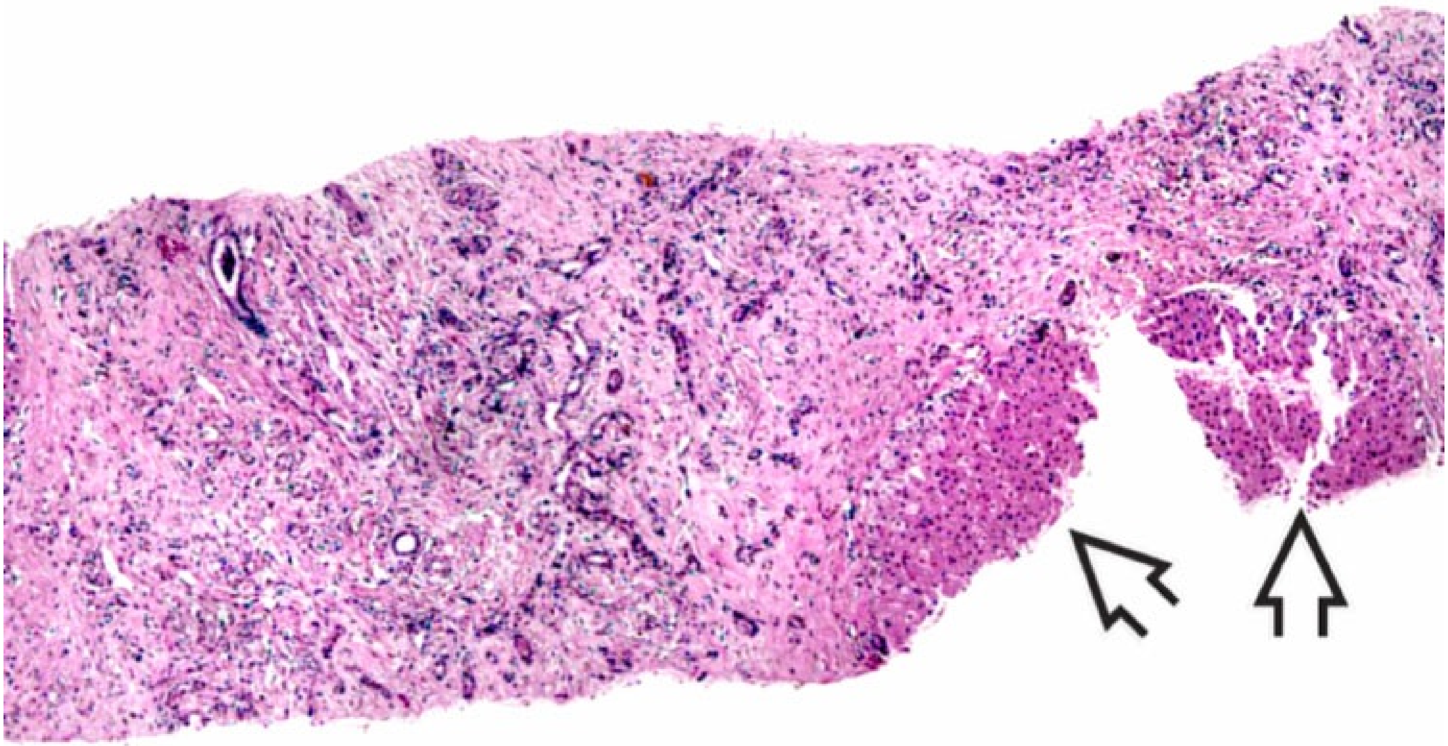
Expanded Portal Tract
At low power, this liver biopsy from a patient with cystic fibrosis shows irregular proliferating bile ductules embedded in an expanded, fibrotic portal tract. Abnormal pink-to-brown secretions (concretions) → can be seen within the ductules.



Ductules With Abnormal Secretions
The ductular reaction can be very pronounced. Abnormal secretions (concretions) → can be seen within the ductules. Note the surrounding fibrosis as well.



Inspissated Eosinophilic Secretions
High-power view shows a portal tract with numerous bile ductules containing inspissated, amorphous, eosinophilic secretions ➭ .



Multilobular Biliary Cirrhosis
Expanded fibrotic portal tracts may ultimately become confluent, producing irregular zones of fibrosis with proliferated, dilated bile ductules. A nodule of liver parenchyma ⇨ is seen on the right. This pattern may be referred to as multilobular biliary cirrhosis.

TERMINOLOGY

Abbreviations

- Cystic fibrosis (CF)

Synonyms

- Mucoviscidosis

Definitions

- Generalized inherited disorder of exocrine gland function
  - Impairs clearance of secretions in multiple organs
  - Abnormal chloride transport in apical membrane of epithelial cells
  - Mutation of *CFTR* gene on chromosome 7
- As life expectancy increases, hepatobiliary disease in CF more often recognized

CLINICAL ISSUES

Epidemiology

- Incidence
  - Most common autosomal recessive disorder
  - Most common lethal autosomal recessive disease in Caucasian population
- 1 in 2,000-2,500 live births
- Ethnicity
  - Caucasian

Presentation

- Respiratory complaints common
  - Recurrent bronchitis and asthma
  - Recurrent respiratory tract infections
- Infants usually present with steatorrhea, bowel obstruction
- Patients rarely initially present with liver disease
  - Liver disease appears to peak during late childhood, adolescence
    - Up to 40% of affected adolescents have evidence of liver disease
  - Clinically silent cirrhosis reportedly seen in ~ 3% of children under 12

Laboratory Tests

- Intermittent elevation of transaminases, alkaline phosphatase
- Elevated sweat chloride level
- Genetic mutational analysis

Treatment

- No specific therapy for liver disease
  - Cirrhosis accounts for virtually all nonpulmonary deaths in CF
- Ursodeoxycholic acid helps some patients
- Management of portal hypertension, liver transplantation in cirrhotic patients

Prognosis

- Chronic disease, but improved therapy has lengthened survival enormously
- Course of liver disease very variable

MACROSCOPIC

General Features

- Depressed white areas of fibrosis in focal biliary fibrosis
- Cirrhosis in patients with end-stage liver disease

MICROSCOPIC

Histologic Features

- Focal biliary fibrosis
  - Proliferated, dilated bile ductules
  - Atrophy of biliary epithelium
  - Ductules contain inspissated eosinophilic secretions/concretions
  - Concretions represent abnormal secretions of CF; PAS positive (diastase resistant); mucicarmine and Alcian blue negative
  - Ducts may rupture, producing inflammatory response
  - Fibrous, expanded portal tracts with variable inflammation
  - Large intrahepatic ducts may contain excessive mucus
  - Steatosis present in up to 1/3 of cases; probably related to malnutrition, fatty acid deficiency
- Focal biliary fibrosis varies in extent, distribution
- With progression, focal lesions become confluent
  - Although not strictly “cirrhosis,” the term “multilobular biliary cirrhosis” is used in this context
  - Liver failure, portal hypertension may develop
- Neonatal CF may show features of neonatal (giant cell) hepatitis
- Some patients have extrahepatic biliary strictures, microgallbladder

Predominant Pattern/Injury Type

- Abnormal secretion

Predominant Cell/Compartment Type

- Bile ductule

DIFFERENTIAL DIAGNOSIS

Primary Sclerosing Cholangitis

- ERCP findings of CF may mimic primary sclerosing cholangitis, which lacks secretions and other clinical findings of CF

Neonatal Hepatitis of Other Causes

- Rule out infection, neonatal biliary diseases

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Liver disease associated with other clinical features of CF
    - Pulmonary disease &/or pancreatic insufficiency

Pathologic Interpretation Pearls

- Focal biliary fibrosis lesion is virtually pathognomonic

SELECTED REFERENCES

1. Lavelle, LP, et al. Cystic fibrosis below the diaphragm: abdominal findings in adult patients. *Radiographics*. 2015; 35(3):680–695.
2. Leung, DH, et al. Baseline ultrasound and clinical correlates in children with cystic fibrosis. *J Pediatr*. 2015; 167(4):862–868.e2.
3. Lykavieris, P, et al. Neonatal cholestasis as the presenting feature in cystic fibrosis. *Arch Dis Child*. 1996; 75(1):67–70.
4. Hultcrantz, R, et al. Morphological findings in the liver of children with cystic fibrosis: a light and electron microscopical study. *Hepatology*. 1986; 6(5):881–889.
5. Oppenheimer, EH, et al. Pathology of cystic fibrosis review of the literature and comparison with 146 autopsied cases. *Perspect Pediatr Pathol*. 1975; 2:241–278.

Hereditary Hemochromatosis

KEY FACTS

Terminology

- Inherited, autosomal recessive disorder of iron metabolism
- Extremely variable penetrance and phenotypic expression

Etiology/Pathogenesis

- Most common mutations are in *HFE* gene
  - 2 most common mutations (C282Y and H63D) account for vast majority of cases
- Non- *HFE*- associated hereditary hemochromatosis occurs less commonly (5-10% of phenotypic cases)
- Specific mechanism leading to iron overload in HH is still unknown

Clinical Issues

- Most patients are of Northern European ancestry
  - Highly variable clinical presentation
  - Presenting signs/symptoms include weakness, evidence of liver disease, cardiac dysfunction, diabetes, skin hyperpigmentation
- Phlebotomy is mainstay of treatment
- Patients are at increased risk for hepatocellular carcinoma, even in absence of cirrhosis and adequate iron-depletion therapy

Macroscopic

- Dark, rusty brown discoloration

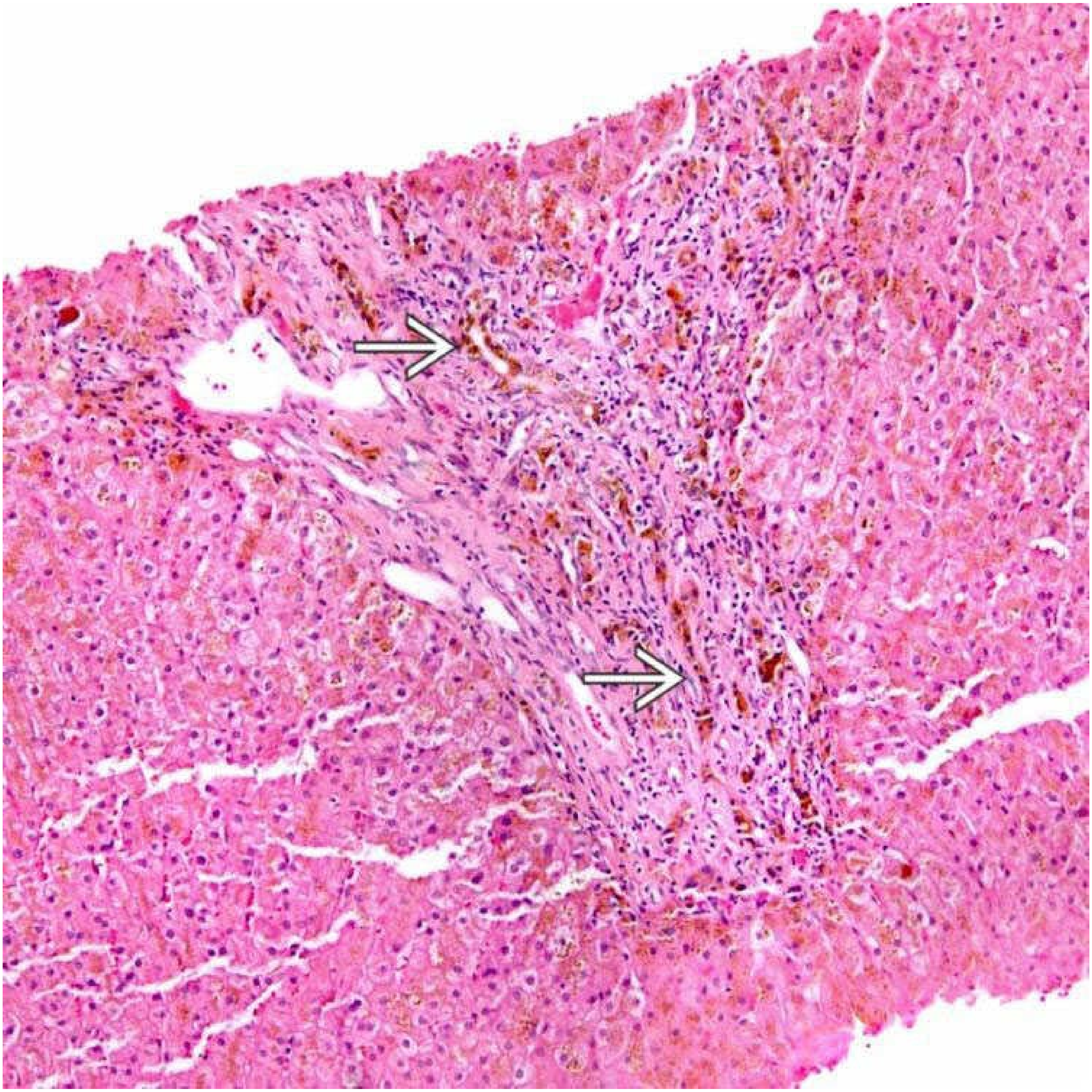
Microscopic

- Iron deposition is characteristic feature
  - Initially in zone 1 hepatocytes, but progresses to involve all zones
  - May also be present in macrophages, biliary epithelium

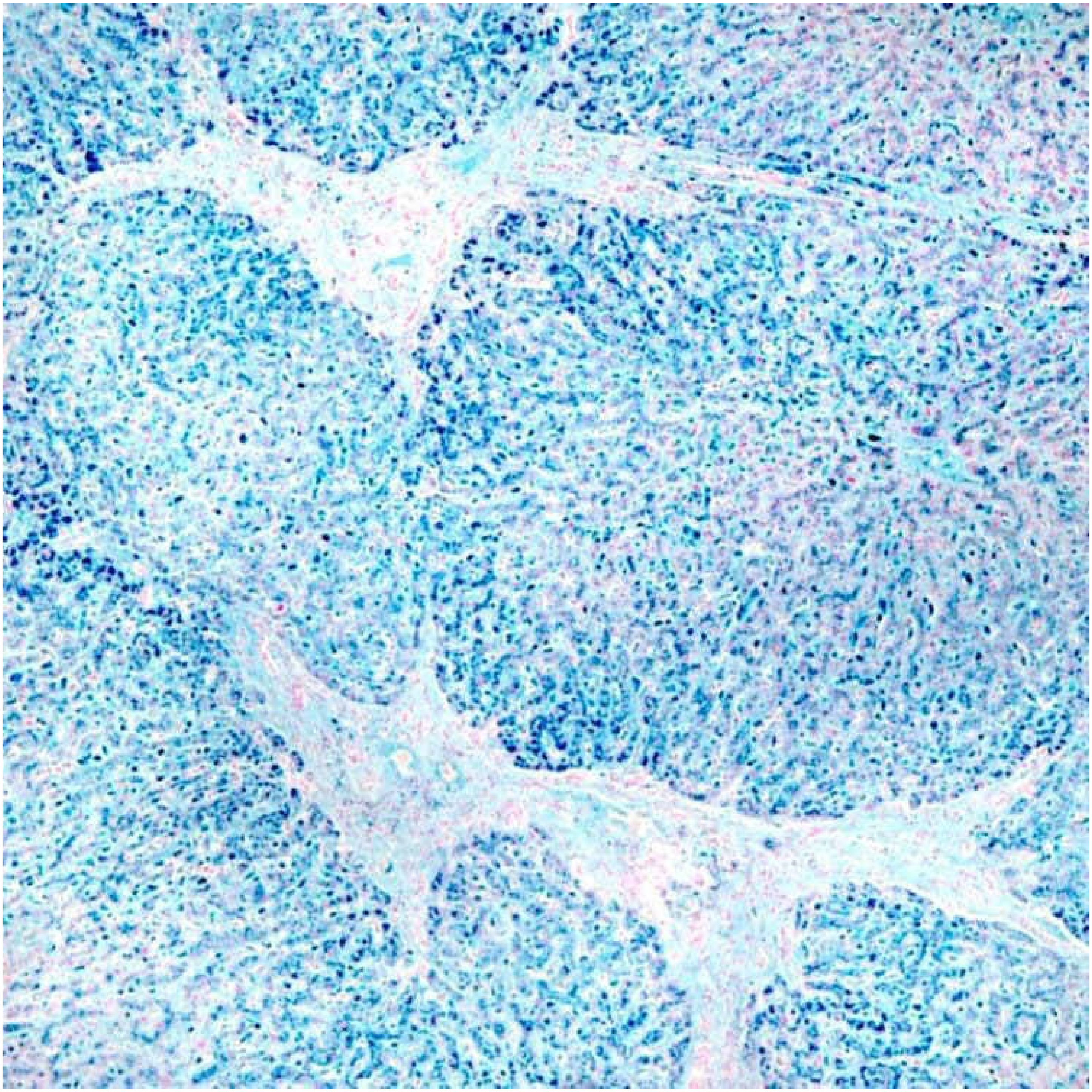
Ancillary Tests

- Molecular testing for individual mutations
- Liver biopsy with measurement of quantitative iron and hepatic iron index
- Serum iron indices

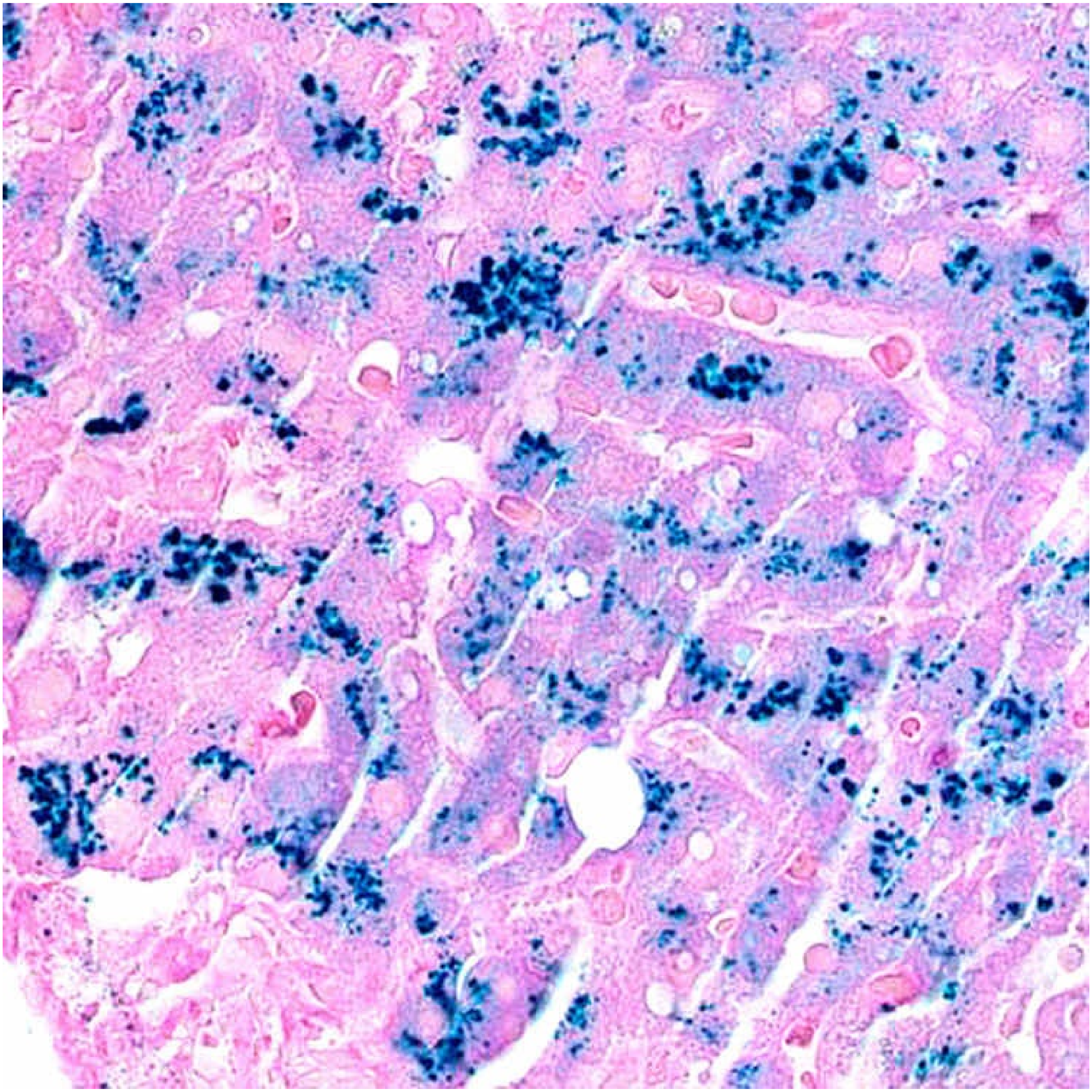
Gross Appearance
This liver obtained from a hereditary hemochromatosis (HH) patient at autopsy shows the characteristic rust-brown color that is typical of increased iron deposition. (Courtesy G. Gray, Jr., MD.)



Periportal Iron Deposition
Iron deposition is visible on a routine H&E stain from this biopsy. Note the periportal iron deposition as well as iron in the bile ducts and ductules ⇒ .



Iron Stain, Cirrhosis
Prussian blue iron stain highlights extensive iron deposition in the hepatocytes of cirrhotic nodules, as well as in the Kupffer cells.



Iron Stain, Pericanalicular Pattern
Perl iron stain shows the pericanalicular pattern of iron deposition in the hepatocytes, typical of most HH.

TERMINOLOGY

Abbreviations

- Hereditary hemochromatosis (HH)

Definitions

- Inherited, autosomal recessive disorder of iron metabolism
  - Extremely variable penetrance and phenotypic expression

ETIOLOGY/PATHOGENESIS

Genetic Mutations

- 2 most common mutations are in *HFE* gene
  - C282Y/C282Y homozygotes
  - – 80-85% of phenotypic cases

- Compound C282Y/H63D heterozygotes

– 5% of phenotypic cases

- Non- *HFE*- associated HH occurs less commonly
  - 5-10% of phenotypic cases
  - TFR2 (transferrin receptor) mutations
  - Ferroportin mutations
  - Juvenile hemochromatosis
    - – Rare
    - – Progresses rapidly and leads to significant disease before age 30
    - – Lower frequency of liver disease
- Specific mechanism leading to iron overload in HH is still unknown

CLINICAL ISSUES

Epidemiology

- Incidence
  - Worldwide allele frequencies
  - – C282Y: 1.9%
  - – H63D: 8.1%
- Ethnicity
  - Most often Northern European origin
    - – C282Y frequency higher in Irish individuals
    - – H63D frequency higher in Basque individuals

Presentation

- 4 clinical stages
  - Genetic predisposition with no clinical or laboratory abnormality
  - Mild iron overload without clinical abnormality
  - Iron overload with early clinical symptoms
  - Iron overload with organ damage
- Highly variable clinical presentation
  - Generalized weakness (60%)
  - Liver disease (13-60%)
  - Diabetes mellitus (10-30%)
  - Cardiac dysfunction (15-35%)
  - Skin pigmentation (47%)

- Sexual dysfunction (10-40%)

- Symptoms may be vague &/or nonspecific
  - Diagnosis may be missed if index of suspicion is not high
- Prevalence of alcoholic liver disease and hepatitis C appears increased in patients with HH

Laboratory Tests

- Transferrin saturation (> 45%)
  - Unbound iron binding capacity (< 28 μmol/L)
  - Serum ferritin (> 300 μg/L in men and 200 μg/L in women)
  - Liver biopsy with quantitative iron determination and calculation of hepatic iron index
  - Can be performed directly from paraffin block

Treatment

- Phlebotomy
  - Mainstay of therapy
  - – Weekly until lab values are desirable, then maintenance over lifetime
- Avoidance of iron-rich foods and supplements
- Chelation therapy
  - Only recommended if phlebotomy is not option
- Liver transplantation for advanced liver disease
  - Outcome complicated by cardiac dysfunction, recurrence in patients with hepatocellular carcinoma (HCC)

Prognosis

- Numerous significant complications
  - Cirrhosis/liver failure
  - HCC
  - – Associated with longstanding HH and cirrhosis
  - Cases have also been reported in noncirrhotic livers

– Risk may persist despite adequate iron-depletion therapy

- Heart failure
- Impotence

- Some studies have shown decreased life expectancy for homozygotes with clinical disease, whereas others have shown no significant decrease in life expectancy

IMAGING

MR Findings

- Can provide accurate estimate of iron overload

MACROSCOPIC

General Features

- Dark, rusty brown discoloration
- Hepatosplenomegaly
- Cirrhosis

MICROSCOPIC

Histologic Features

- Iron deposition
    - Initially in periportal (zone 1) hepatocytes
    - Progressively involves all zones
    - Iron often pericanalicular in distribution
        - Iron may also be present in biliary epithelium
    - Deposition of iron in Kupffer cells is nonspecific
        - Can occur in HH, as well as secondary causes of iron overload
        - Some patients with HH due to ferroportin mutations show predominantly Kupffer cell deposition
    - Iron stain highlights pigment accumulation
    - Several grading schemes exist for evaluating iron deposition
        - Scheuer scheme (estimation of overall iron with assignment of grade 1-4) is most often used in routine practice
- Associated portal and lobular chronic inflammation
- Fibrosis is initially portal based
    - Progresses to periportal fibrosis, bridging, and eventually cirrhosis
- Iron-free foci in advanced HH may be early harbinger of HCC

Hereditary Hemochromatosis

Type	Age	Mutated Gene	Genotype	Pattern of Iron Deposition
1	Adult	*HFE*	C282Y/C282YC282Y/H63D	Hepatocellular with periportal accentuation
2A	Juvenile	Hemojuvelin		Hepatocellular with periportal accentuation
2B	Juvenile	Hepcidin		Hepatocellular with periportal accentuation
3	Adult	Transferrin receptor 2		Hepatocellular with periportal accentuation
4	Adult	Ferroportin		A. Kupffer cell and hepatocytes
				B. Predominantly hepatocellular

ANCILLARY TESTS

PCR

- Testing blood for individual mutations

DIFFERENTIAL DIAGNOSIS

Anemia of Chronic Disease

- Iron deposition in both hepatocytes and Kupffer cells

Transfusion-Related Hemosiderosis

- Iron deposition in Kupffer cells in early stages
- May accumulate in hepatocytes when excessive

Chronic Hemolytic Disorders

- Iron deposition in both hepatocytes and Kupffer cells

Other Chronic Liver Diseases

- Nonspecific iron accumulation is common in many other chronic liver diseases
    - Hepatitis C
    - Alcoholic liver disease
    - Nonalcoholic fatty liver disease
- HH may coexist with other chronic liver diseases as well

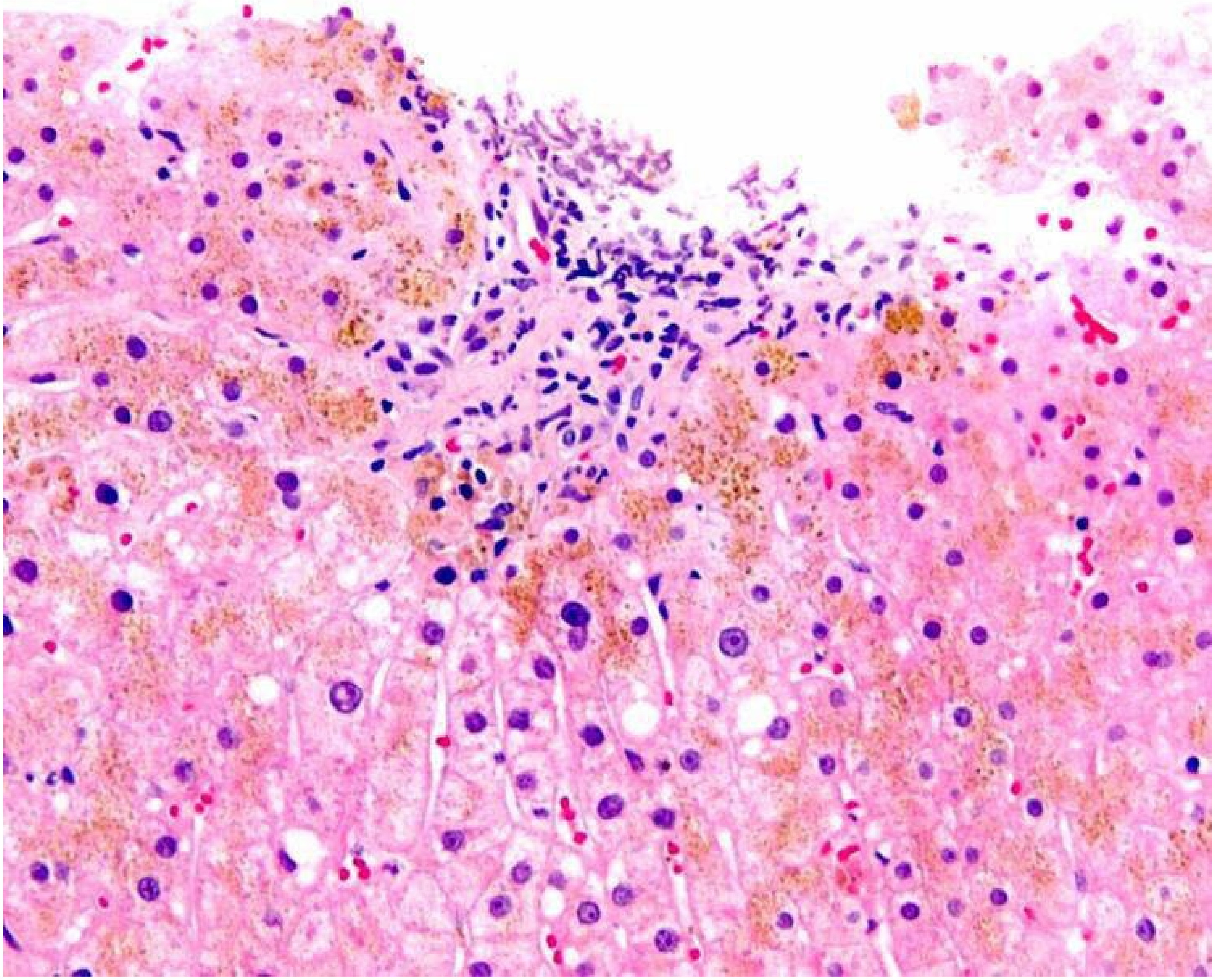
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

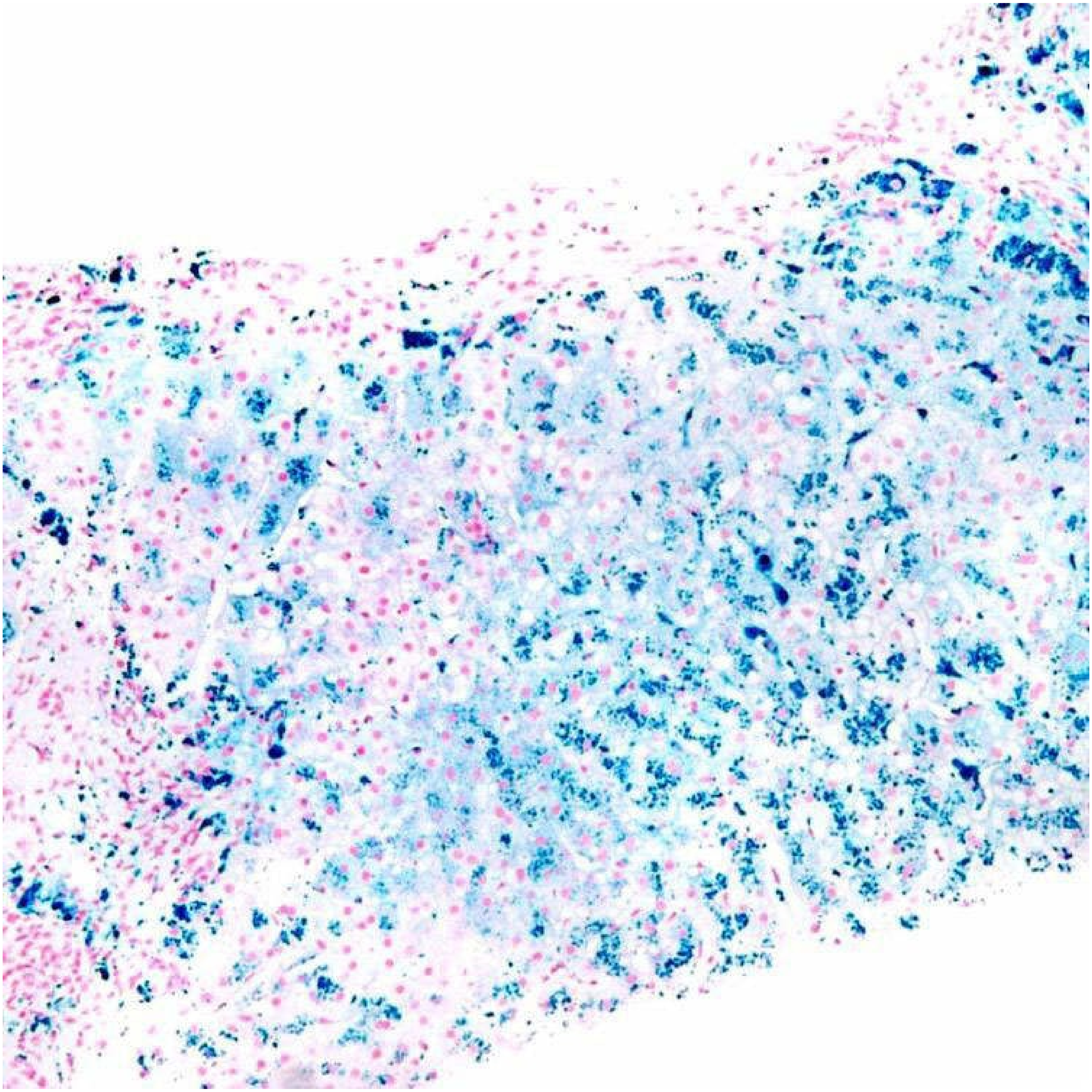
- Increased iron in patients with elevated LFTs
- Other signs/symptoms may be highly variable and nonspecific

Pathologic Interpretation Pearls

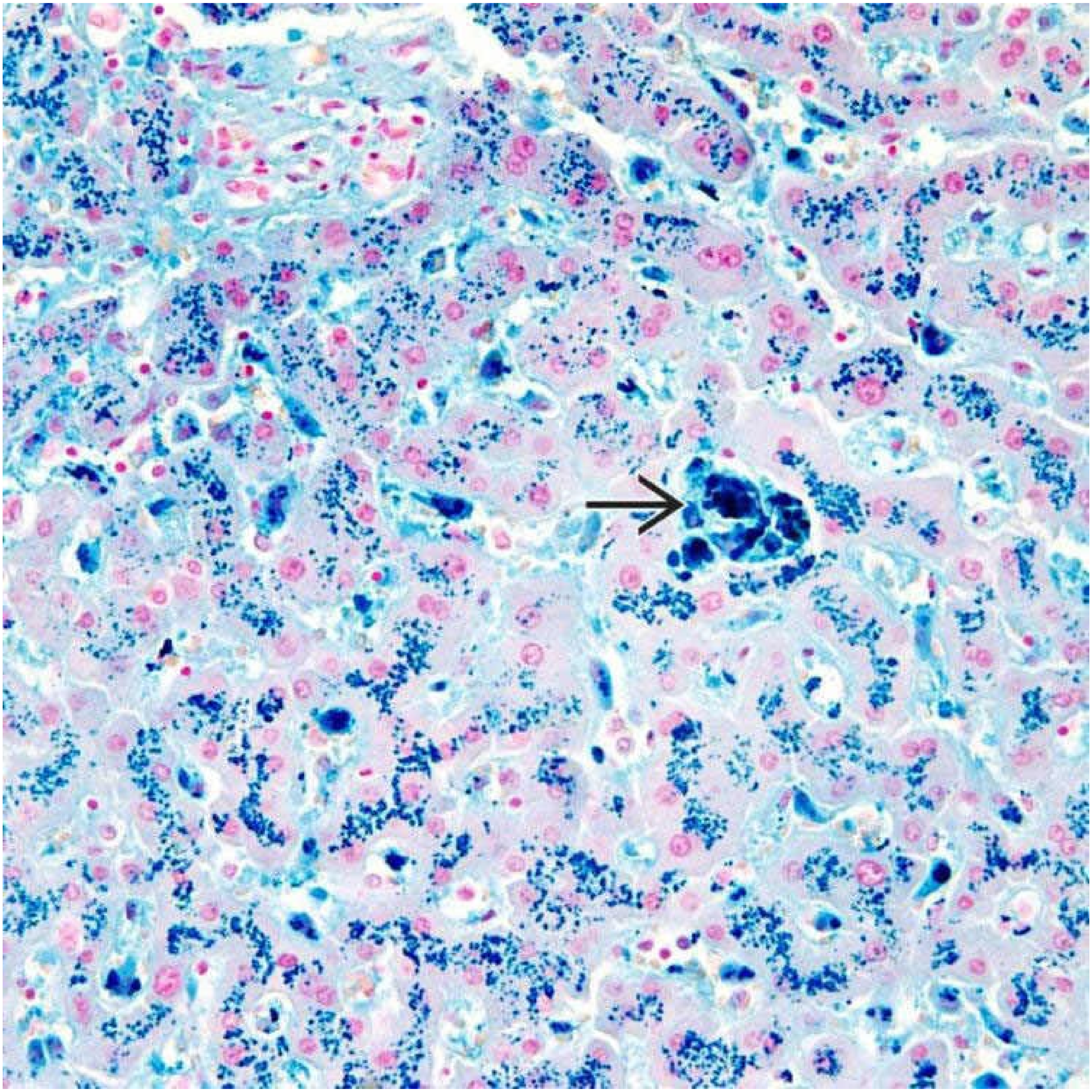
- Recommend genetic testing, quantitative hepatic iron evaluation in patients with histologic iron overload



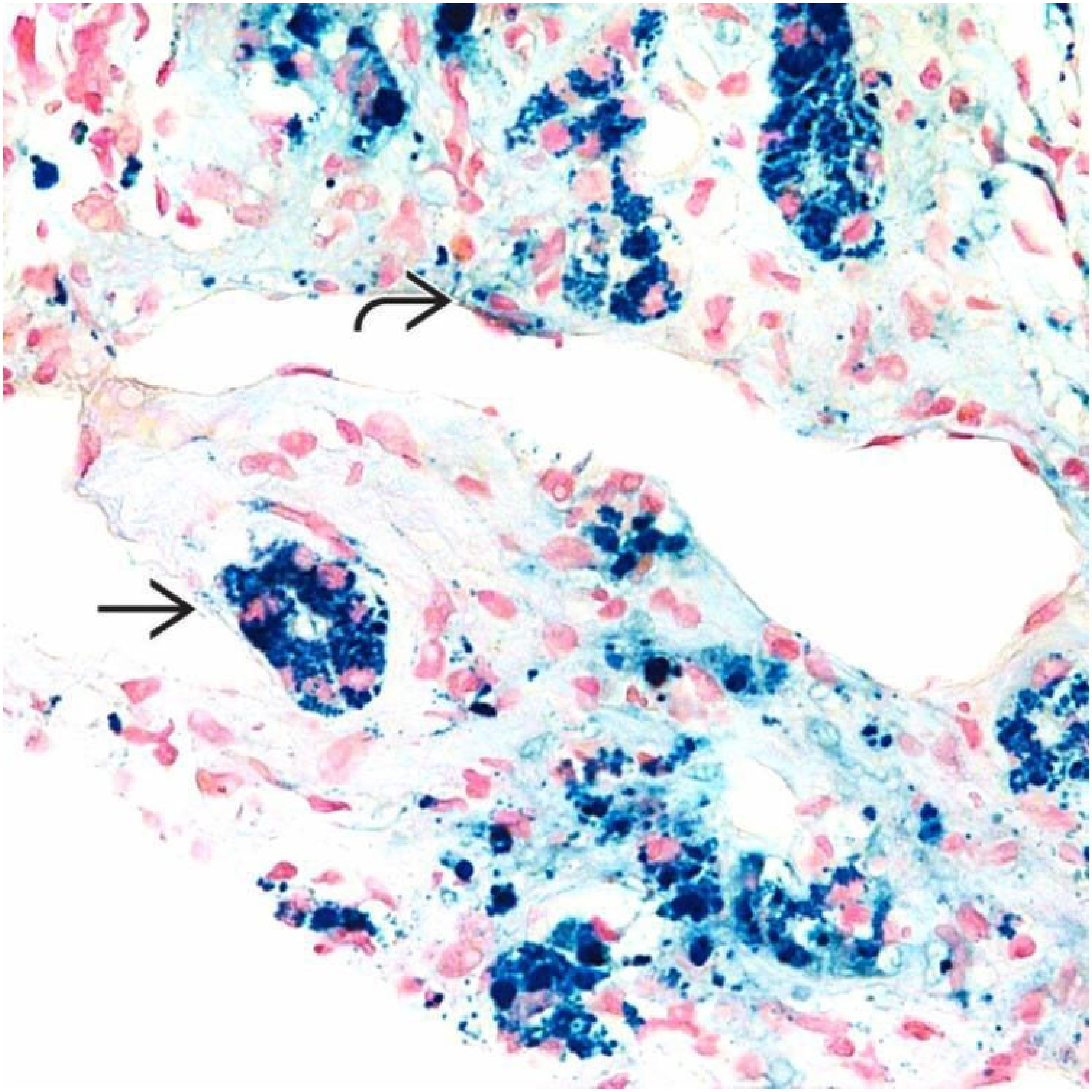
Early Hereditary Hemochromatosis
This biopsy of early HH shows brown, granular iron deposition primarily in a periportal (zone 1) distribution.



Iron Stain, Progression of Iron Deposition
As disease progresses, the iron deposition extends from zone 1 to eventually involve all zones of the liver parenchyma. There is minimal inflammation.

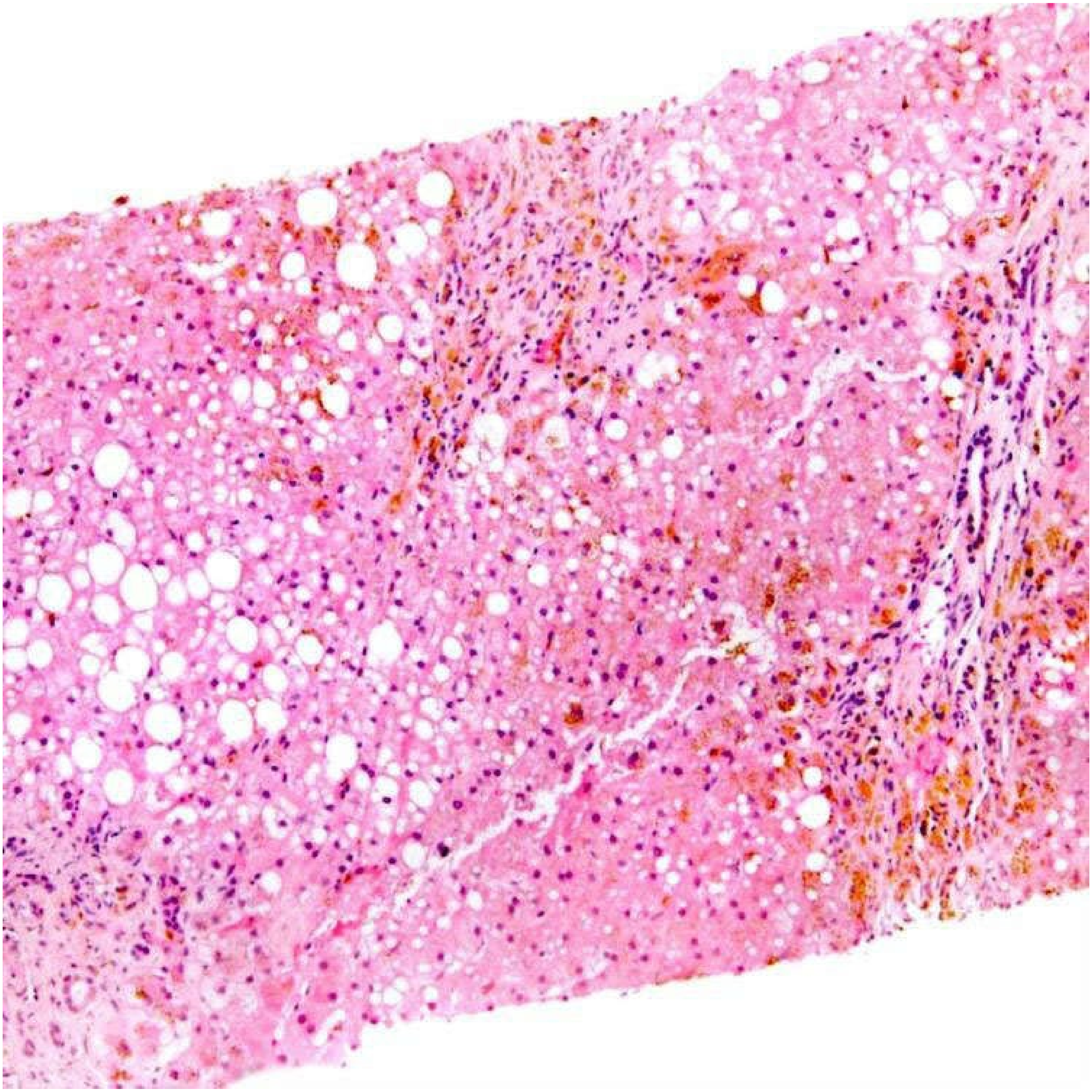


Iron Stain, Medium Power
Iron stain shows extensive iron deposition in both hepatocytes (note pericanalicular pattern of distribution) and macrophages →.

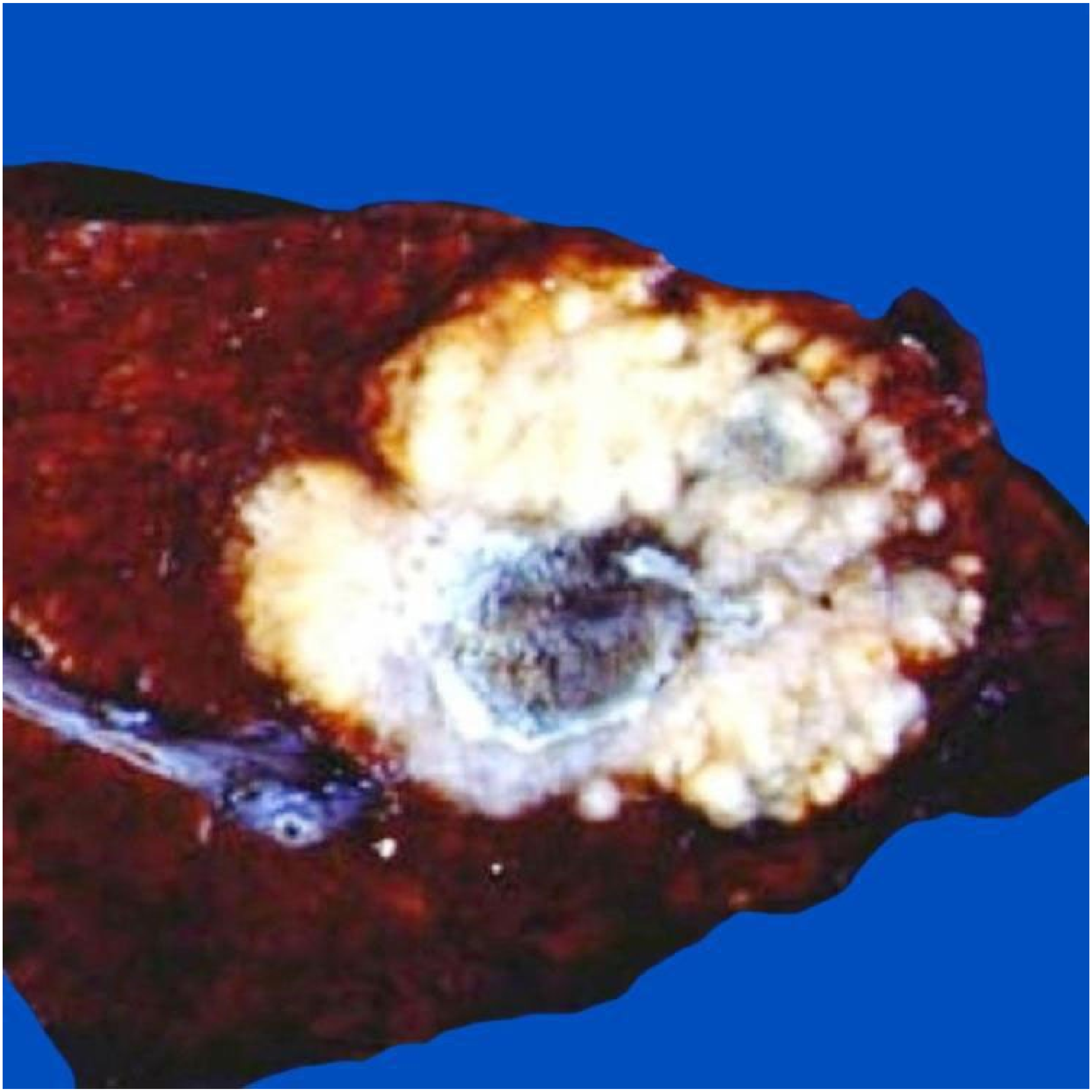


Iron Stain, High Power

Iron stain highlights iron within hepatocytes, macrophages, biliary epithelium →, and endothelium ↱.



Hereditary Hemochromatosis and NASH
This patient has both nonalcoholic fatty liver disease and HH. Note the periportal iron deposition in addition to the features of fatty liver disease.



Hereditary Hemochromatosis and Hepatocellular Carcinoma
This gross specimen shows a necrotic focus of hepatocellular carcinoma arising in a background of HH. Note the rust-brown color of the background liver. (Courtesy G. Gray, Jr., MD.)

SELECTED REFERENCES

1. Kanwar, P, et al. Diagnosis and treatment of hereditary hemochromatosis: an update. *Expert Rev Gastroenterol Hepatol*. 2013; 7(6):517–530.
2. Babitt, JL, et al. The molecular pathogenesis of hereditary hemochromatosis. *Semin Liver Dis*. 2011; 31(3):280–292.
3. Girelli, D, et al. Clinical, pathological, and molecular correlates in ferroportin disease: a study of two novel mutations. *J Hepatol*. 2008; 49(4):664–671.
4. Batts, KP. Iron overload syndromes and the liver. *Mod Pathol*. 2007; 20(Suppl 1):S31–S39.

5. Beaton, MD, et al. Prognostic factors and survival in patients with hereditary hemochromatosis and cirrhosis. *Can J Gastroenterol*. 2006; 20(4):257–260.
6. Brunt, EM. Pathology of hepatic iron overload. *Semin Liver Dis*. 2005; 25(4):392–401.
7. Uraz, S, et al. Serum iron levels and hepatic iron overload in nonalcoholic steatohepatitis and chronic viral hepatitis. *Dig Dis Sci*. 2005; 50(5):964–969.
8. Adams, PC. Hemochromatosis. *Clin Liver Dis*. 2004; 8(4):735–753. [vii].
9. Girelli, D, et al. Clinical and pathologic findings in hemochromatosis type 3 due to a novel mutation in transferrin receptor 2 gene. *Gastroenterology*. 2002; 122(5):1295–1302.
10. Adams, P, et al. EASL International Consensus Conference on Haemochromatosis. *J Hepatol*. 2000; 33(3):485–504.
11. Merryweather-Clarke, AT, et al. Global prevalence of putative haemochromatosis mutations. *J Med Genet*. 1997; 34(4):275–278.
12. Feder, JN, et al. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nat Genet*. 1996; 13(4):399–408.
13. Deugnier, YM, et al. Preneoplastic significance of hepatic iron-free foci in genetic hemochromatosis: a study of 185 patients. *Hepatology*. 1993; 18(6):1363–1369.
14. Lamon, JM, et al. Idiopathic hemochromatosis in a young female. A case study and review of the syndrome in young people. *Gastroenterology*. 1979; 76(1):178–183.

Wilson Disease

KEY FACTS

Etiology/Pathogenesis

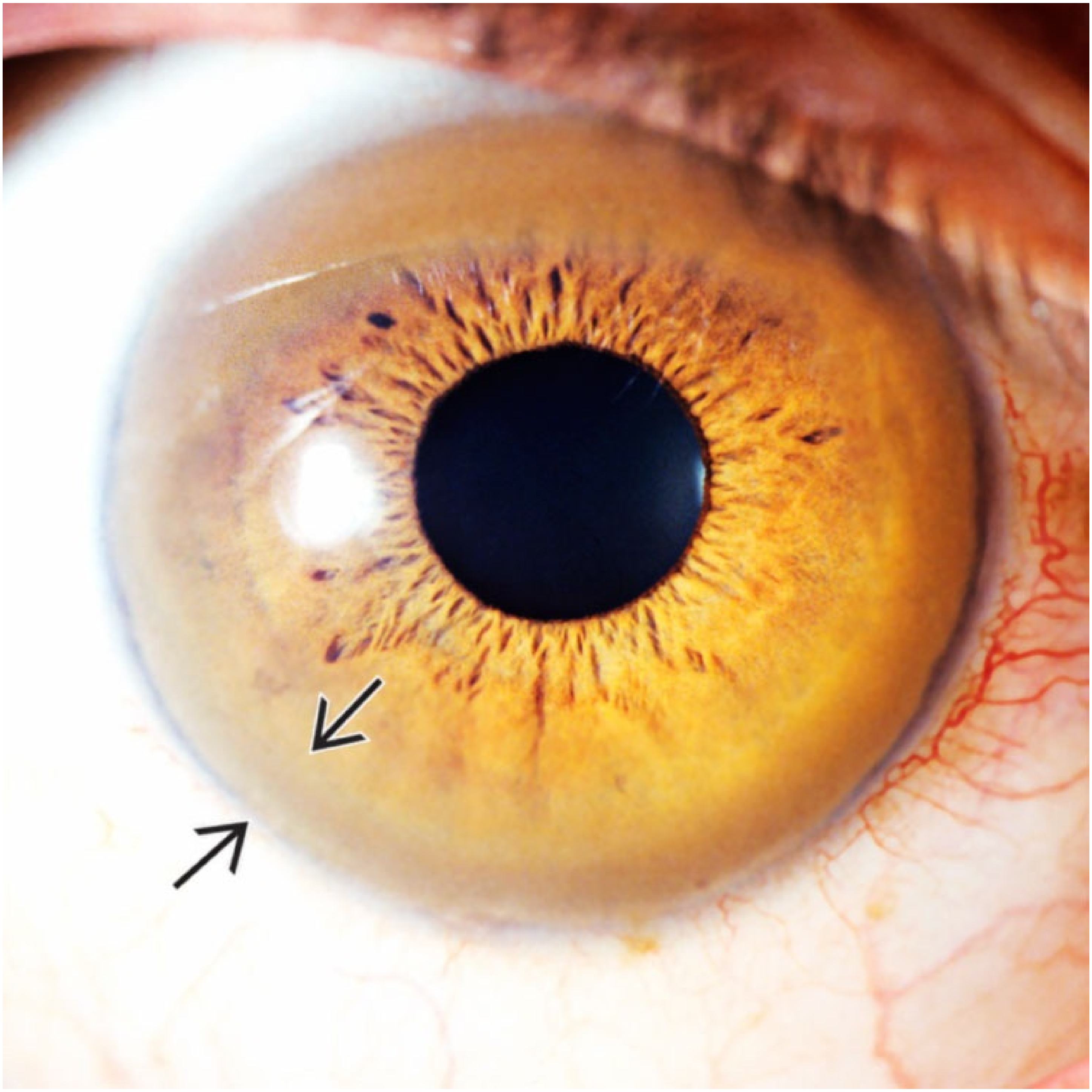
- Mutations of *ATP7B* gene, which codes for copper transport protein found on Golgi apparatus and canalicular membrane
  - Inability to excrete copper in bile leads to its accumulation in liver and other tissues

Clinical Issues

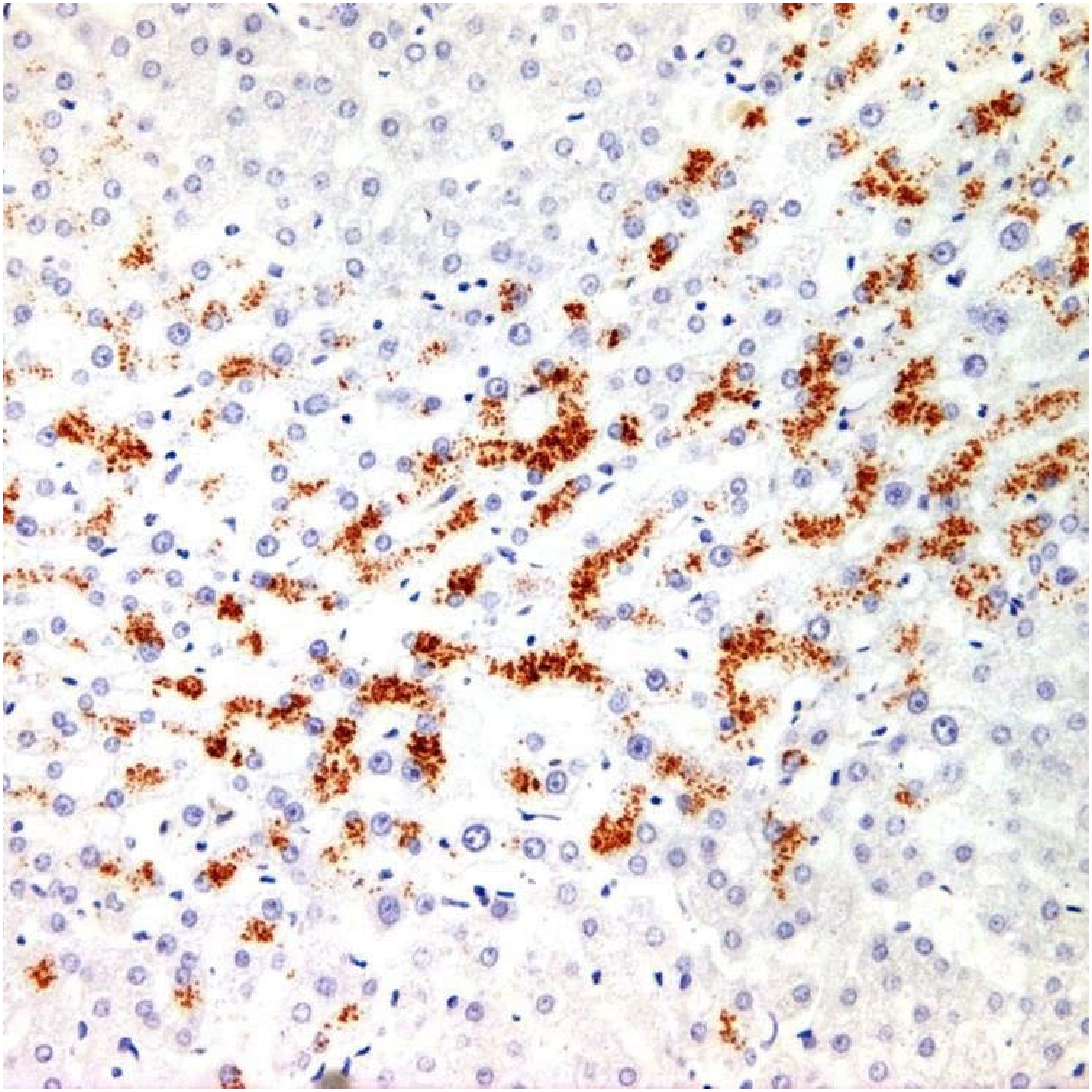
- Variable presentation
  - Acute liver failure, chronic liver disease with fibrosis/cirrhosis, neurologic/neuropsychiatric signs ± Kayser-Fleischer rings
  - Copper chelators and zinc are mainstay of medical therapy
  – Without treatment, progresses to cirrhosis and death
- Increased serum free copper and urinary copper are characteristic
- Increased hepatic copper concentration is most reliable test and is diagnostic in most cases
- Laboratory tests
  - Low serum ceruloplasmin level is characteristic but is neither sensitive nor specific
  - Increased serum free copper and urinary copper
  - Increased hepatic copper concentration is most reliable test

Microscopic

- Early disease is characterized by steatosis, variably present Mallory hyaline, and glycogenated nuclei
  - Intermediate stage is characterized by chronic hepatitis with fibrosis or cirrhosis
  - Histologic features on routine staining are very nonspecific, so diagnosis easily missed
  - Rhodanine or rubeanic acid stains for copper and orcein or aldehyde fuchsin stains for copper-associated protein may be helpful
  - Staining may be very variable within liver; thus negative stain does not exclude disease

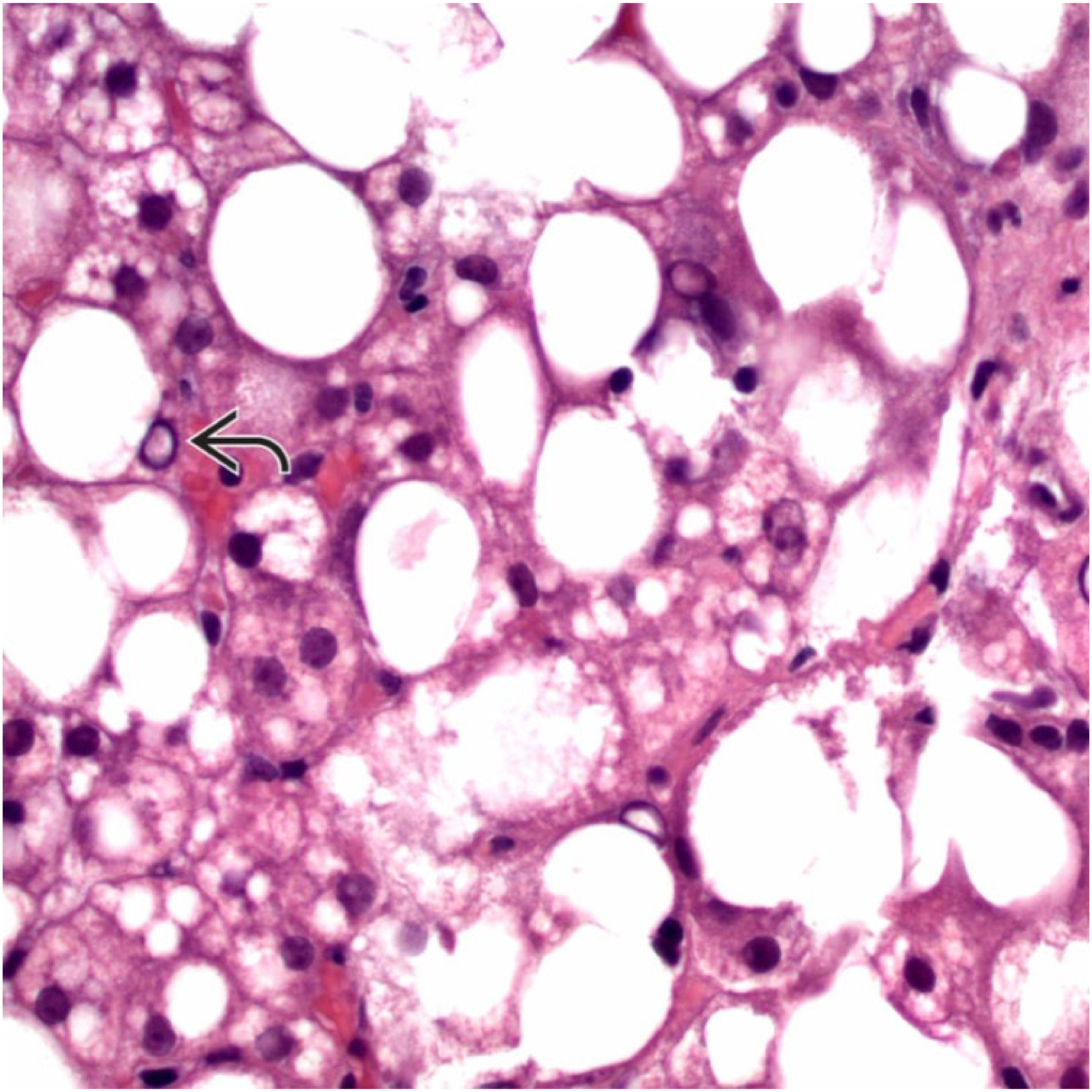


Kayser-Fleischer Ring
Clinical photograph of Kayser-Fleischer ring shows brown deposits of copper at the periphery of the iris →. (Courtesy S. Uwaydat, MD.) Almost half of patients with Wilson disease lack this finding, however.

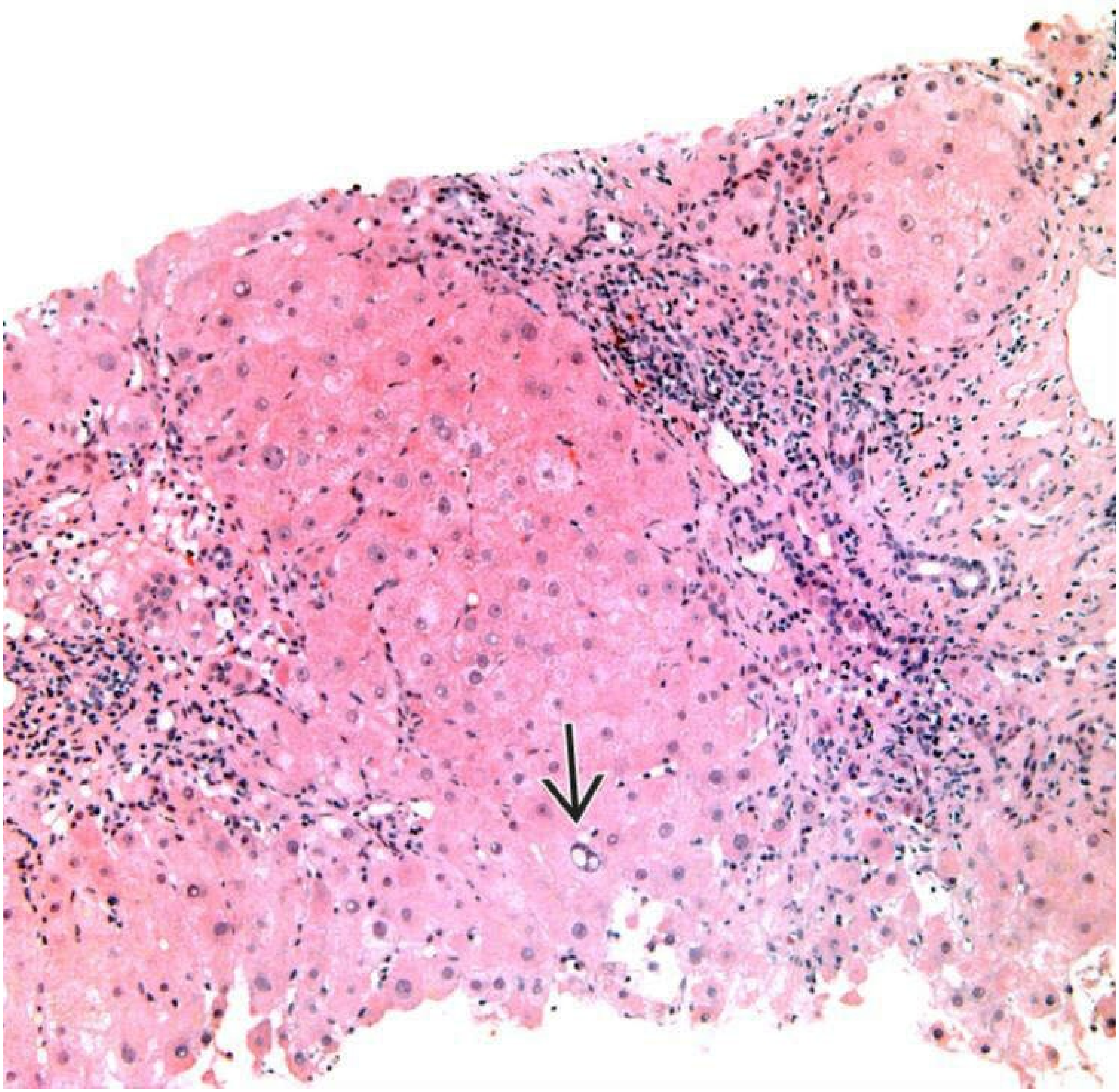


Rhodanine Stain

Red-brown granular staining is seen within hepatocytes on rhodanine stain, characteristic of Wilson disease. However, staining may be focal within the liver, and thus a negative stain does not exclude disease.



Features of Steatohepatitis
Liver biopsies in Wilson disease frequently show features of steatohepatitis, with steatosis and glycogenated nuclei.



Inflammation
Many biopsies from Wilson disease patients show only nonspecific portal-based chronic inflammation, as seen here. Note the rare, large glycogenated nuclei → .

TERMINOLOGY

Synonyms

• Hepatolenticular degeneration

Definitions

• Inherited autosomal recessive inherited mutation of copper transport protein

ETIOLOGY/PATHOGENESIS

Genetic Defect

- Mutations of *ATP7B* gene, which codes for copper-dependent P-type ATPase, copper transport protein found on Golgi apparatus and on canalicular membrane
  - Inability to excrete copper in bile leads to its accumulation in liver and various tissues
  - Inability to transport copper into Golgi apparatus makes it unavailable for synthesis of ceruloplasmin, leading to release of apoceruloplasmin into serum and its rapid degradation
  - – Ceruloplasmin functions as plasma ferroxidase, oxidizing ferrous iron for subsequent transfer to plasma apotransferrin, making it available for hemoglobin biosynthesis

CLINICAL ISSUES

Epidemiology

- Incidence
  - 1 in 30,000

Presentation

- Acute liver failure with Coombs(-) hemolytic anemia and renal failure
- Chronic liver disease with fibrosis or cirrhosis
- Neurologic/neuropsychiatric signs with Kayser-Fleischer rings

Laboratory Tests

- Low ceruloplasmin is characteristic but neither sensitive nor specific
  - Low ceruloplasmin can also be due to low hepatic synthetic function
  - Normal ceruloplasmin levels can be seen in Wilson disease because ceruloplasmin is acute phase reactant
- Increased serum free copper
- Increased urinary copper
- Increased hepatic copper concentration is most reliable test
  - Can be performed on fresh tissue or paraffin block, although fresh tissue more accurate
- Genetic testing is definitive but difficult due to number of mutations
  - Most patients are compound heterozygotes

Treatment

- Drugs
  - Copper chelators (penicillamine, trientine, ammonium tetrathiomolybdate)
  - Zinc induces hepatocytic and intestinal metallothionein; latter results in binding of copper in enterocytes and its loss when enterocytes are shed
- Foods high in copper should be avoided

Prognosis

- Without treatment, progresses to cirrhosis and death
- With treatment, can be managed
- Hepatocellular carcinoma is rare complication
- Transplant is option for patients with acute liver failure or chronic disease not responsive to medical therapy

MICROSCOPIC

Histologic Features

- Early disease is characterized by steatosis, Mallory hyaline, and glycogenated nuclei, mimicking steatohepatitis
- Intermediate stage is characterized by chronic hepatitis with fibrosis or cirrhosis, mimicking viral or autoimmune hepatitis, but with few plasma cells
- Fulminant cases may have severe hepatocyte damage, cholestasis, parenchymal necrosis and collapse

Histochemical Stains

- Rhodanine or rubeanic acid stains stain copper
- Orcein or aldehyde fuchsin stain, copper-associated protein (metallothionein)
- Staining initially involves periportal hepatocytes; may extend to involve entire lobule over time
- Staining may be very variable within liver; thus negative stain does not exclude disease

DIFFERENTIAL DIAGNOSIS

Nonalcoholic Steatohepatitis

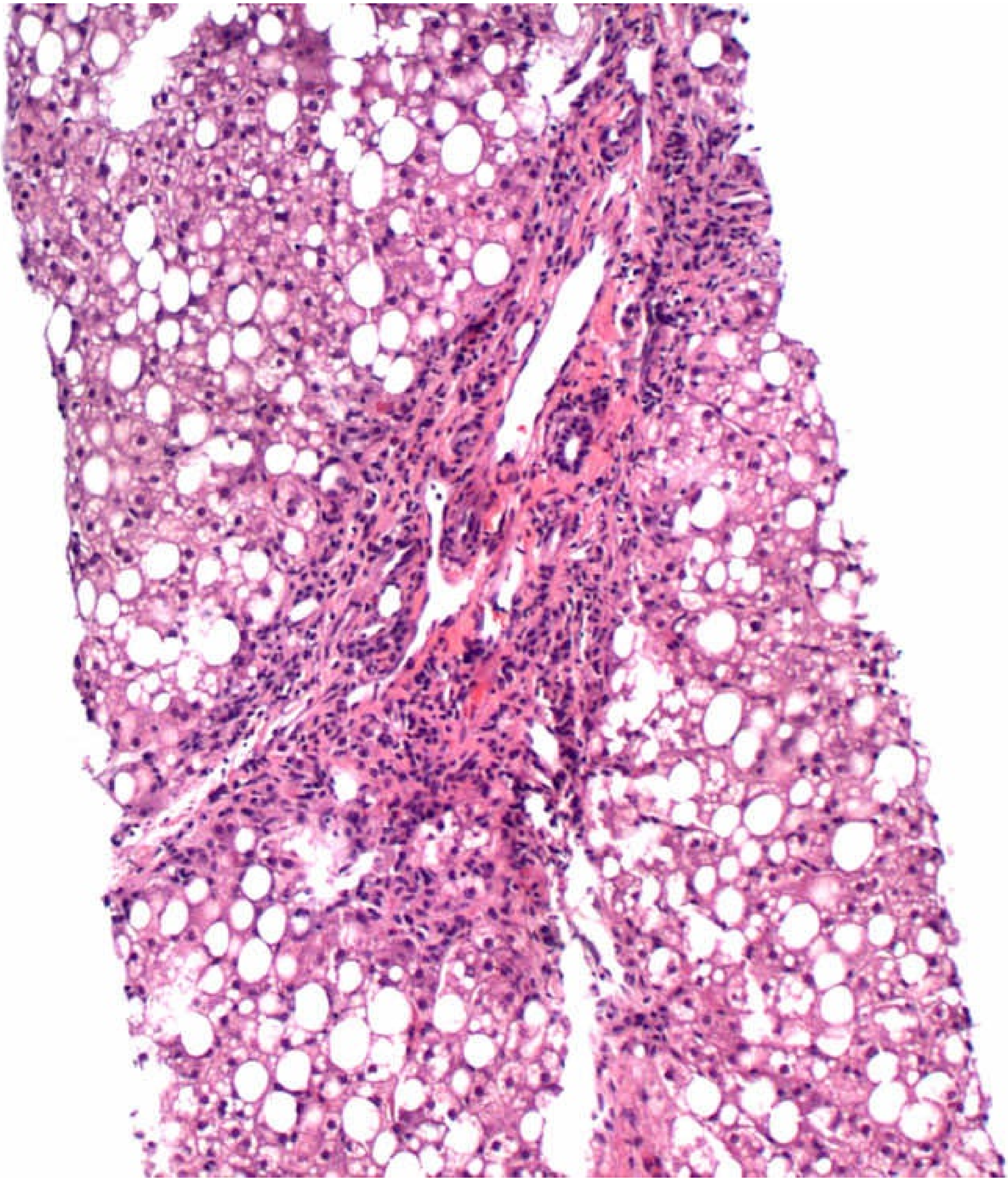
- Clinical features are different
- No tissue or laboratory evidence of accumulated copper

Autoimmune Hepatitis

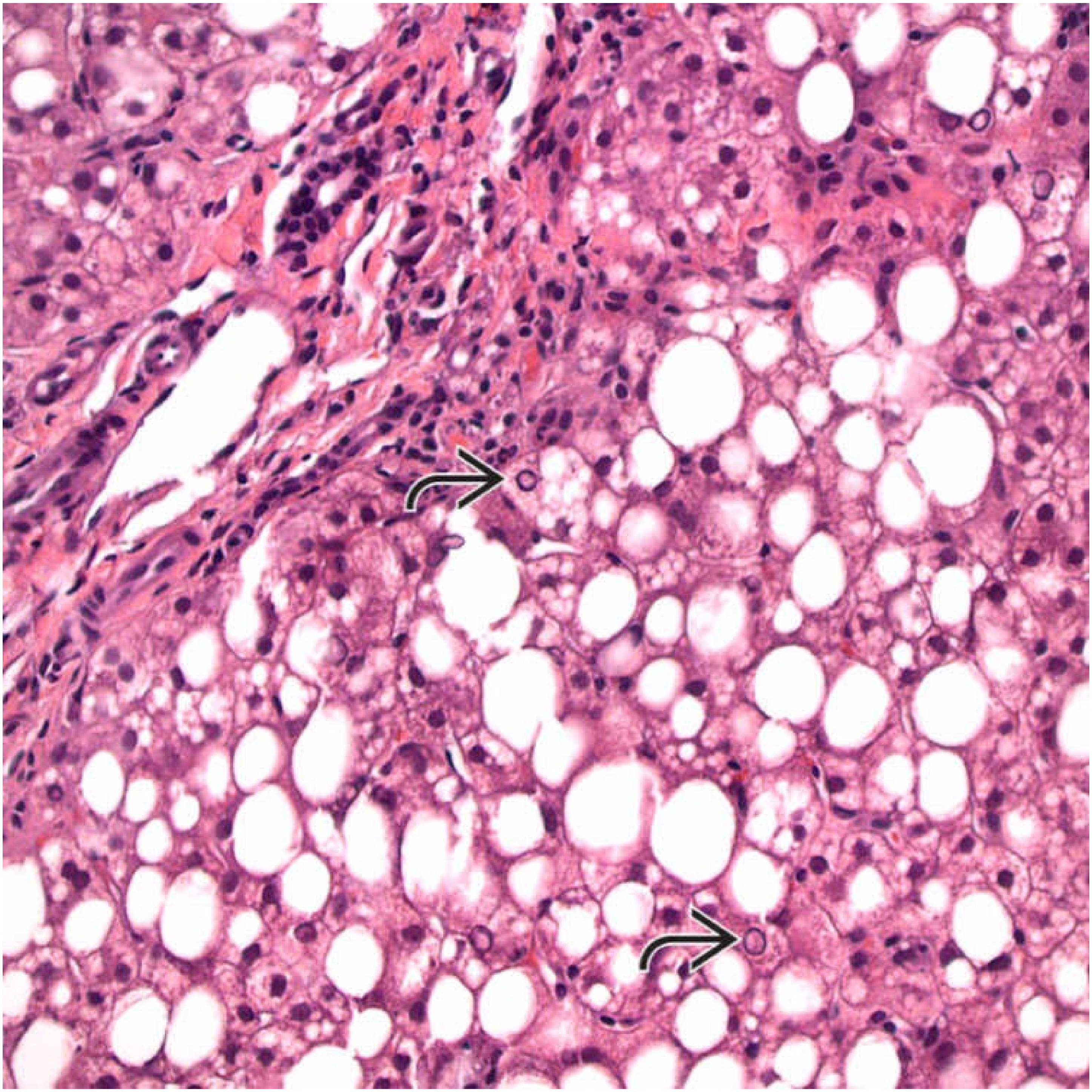
- Numerous plasma cells
- Copper stain is negative
- No tissue or laboratory evidence of accumulated copper
- Autoimmune serologies typically positive

Chronic Cholestatic Diseases

- Copper stain often positive in periportal distribution
  - Quantitative copper measurement in tissue not diagnostic of Wilson disease
- Clinical features are different
- Liver enzymes typically show obstructive pattern

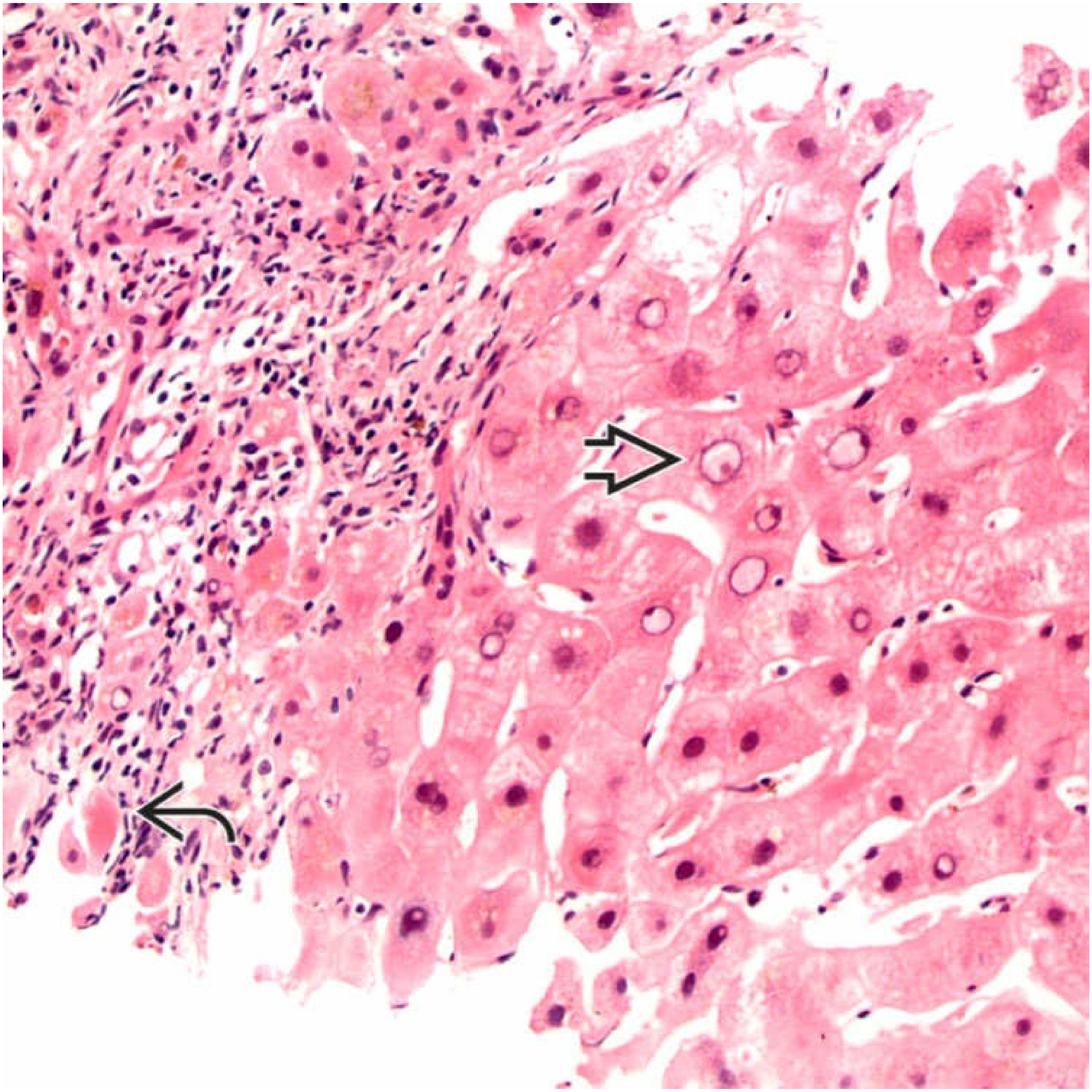


Features of Steatohepatitis
This liver biopsy demonstrates features of steatohepatitis in Wilson disease at low power, including diffuse steatosis and portal expansion.



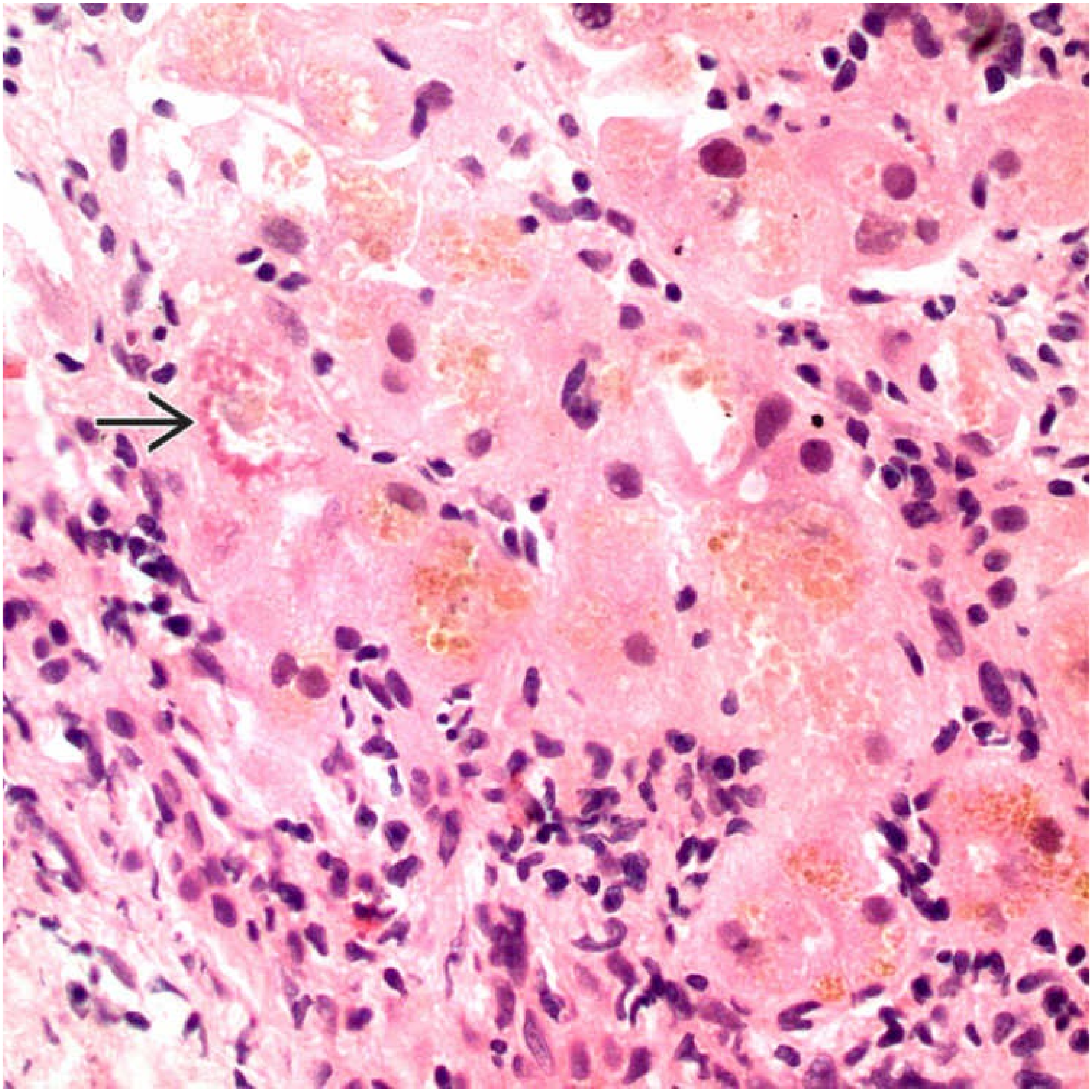
Steatohepatitis

This liver biopsy in Wilson disease shows mixed large and small droplet steatosis and many glycogenated nuclei ↱ .



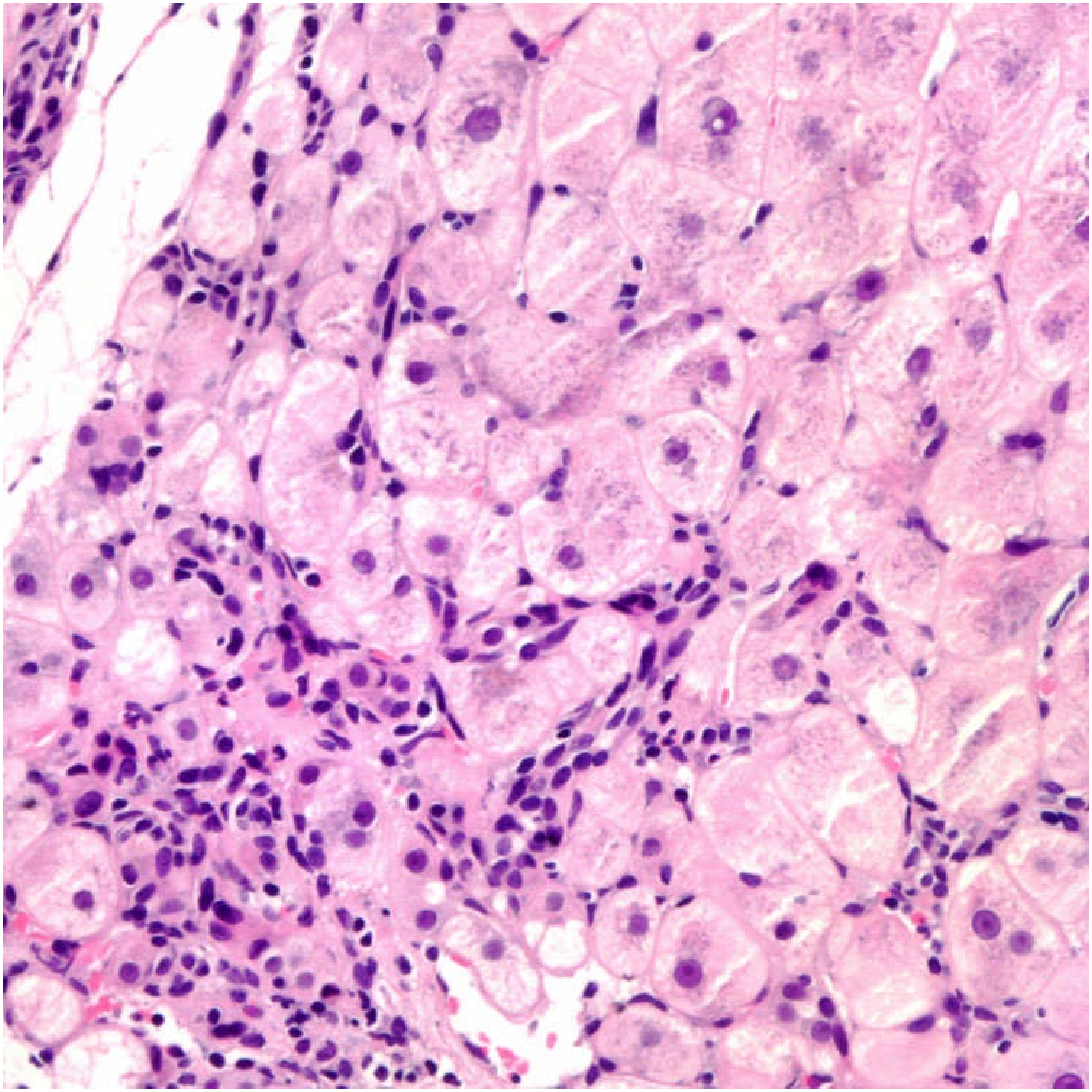
Glycogenated Nuclei

Glycogenated nuclei ➭ are a common feature of Wilson disease. Note the nonspecific portal-based chronic inflammatory infiltrate and scattered necrotic hepatocytes ↷ .

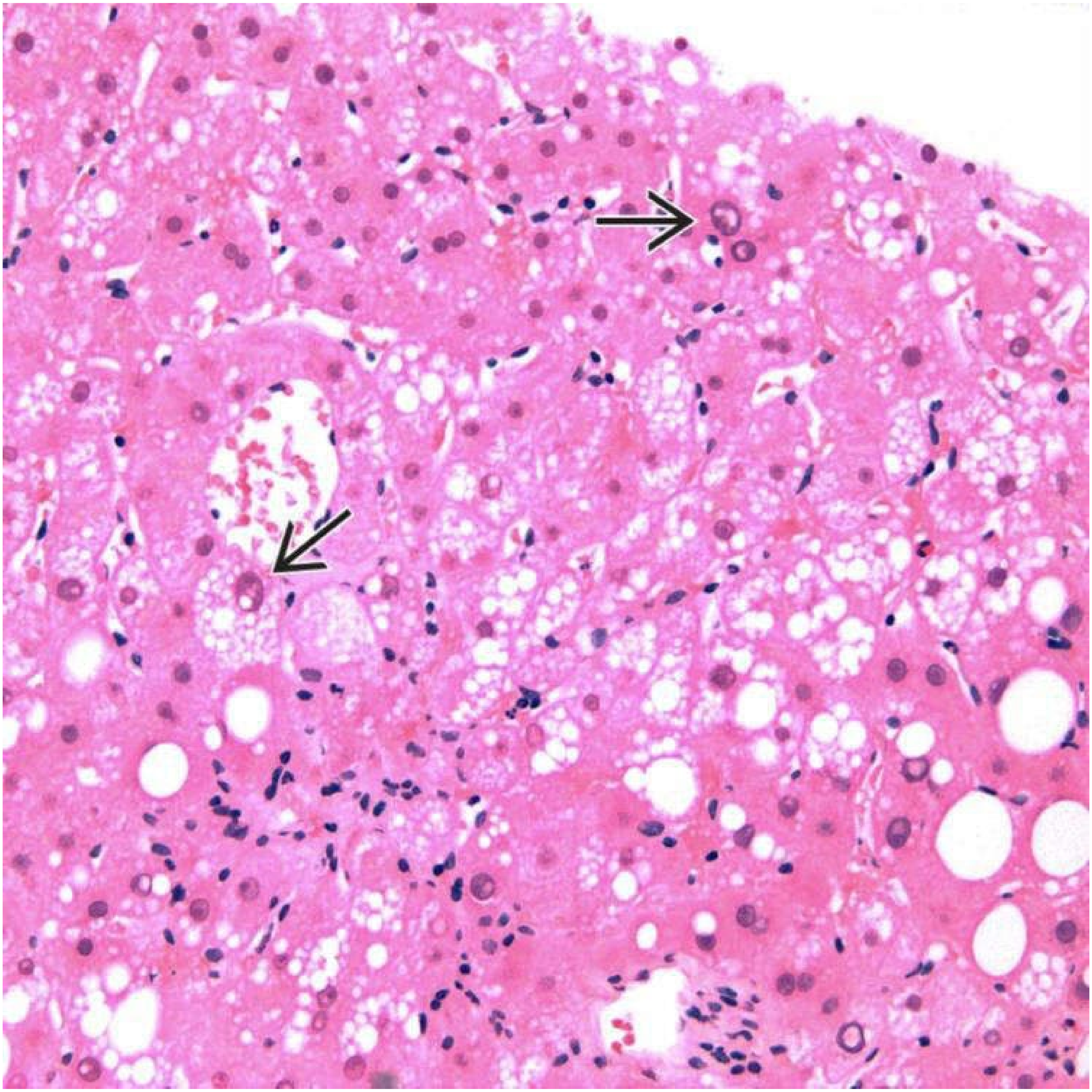


Mallory Hyaline

This biopsy from Wilson disease shows chronic inflammation in periportal parenchyma, increased pigment in hepatocytes, and focal Mallory hyaline →, which can be seen in Wilson disease.

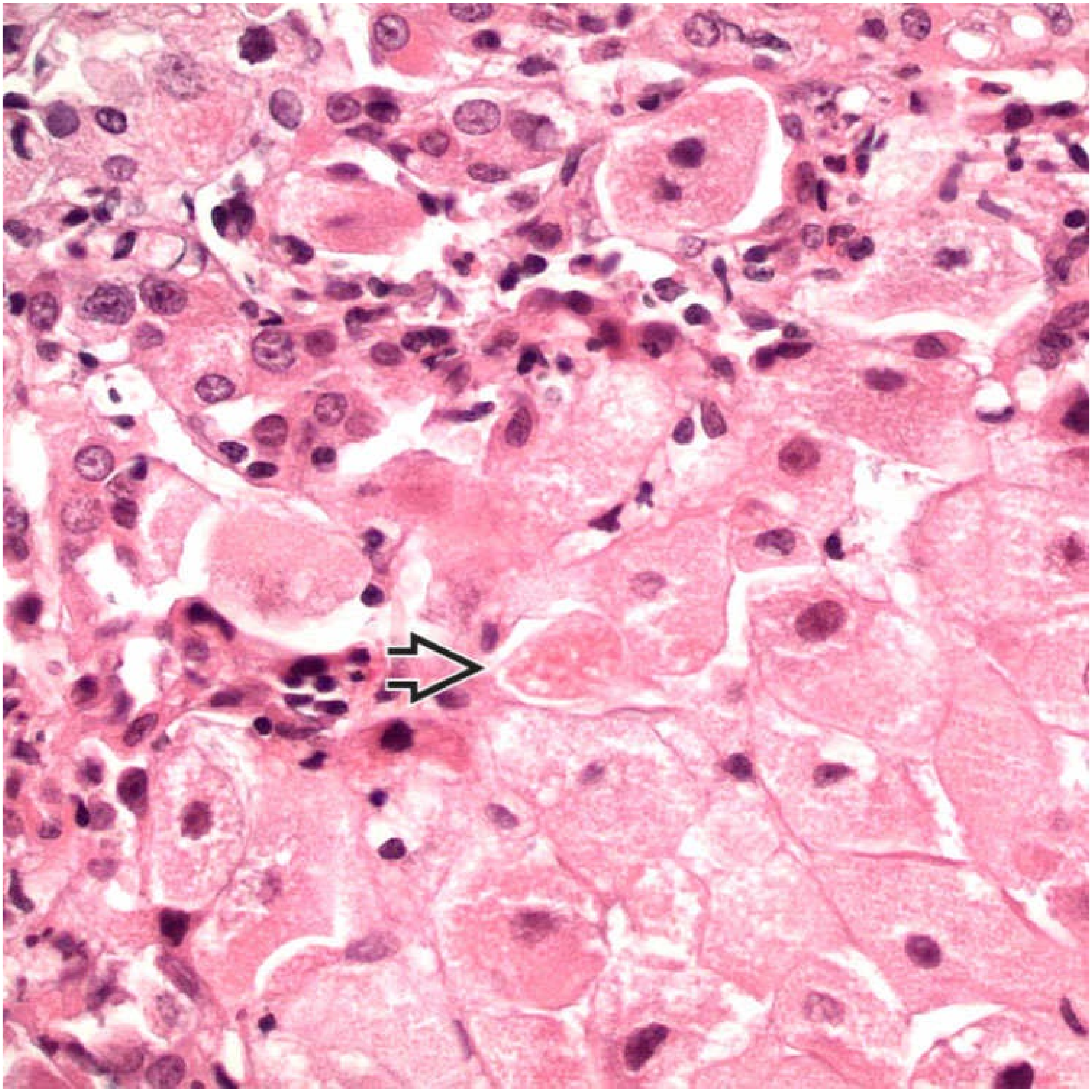


Inflammation
This biopsy in Wilson disease shows nonspecific chronic inflammatory infiltrates and hepatocyte swelling. Note the lack of plasma cells, which helps to distinguish Wilson disease from autoimmune hepatitis.

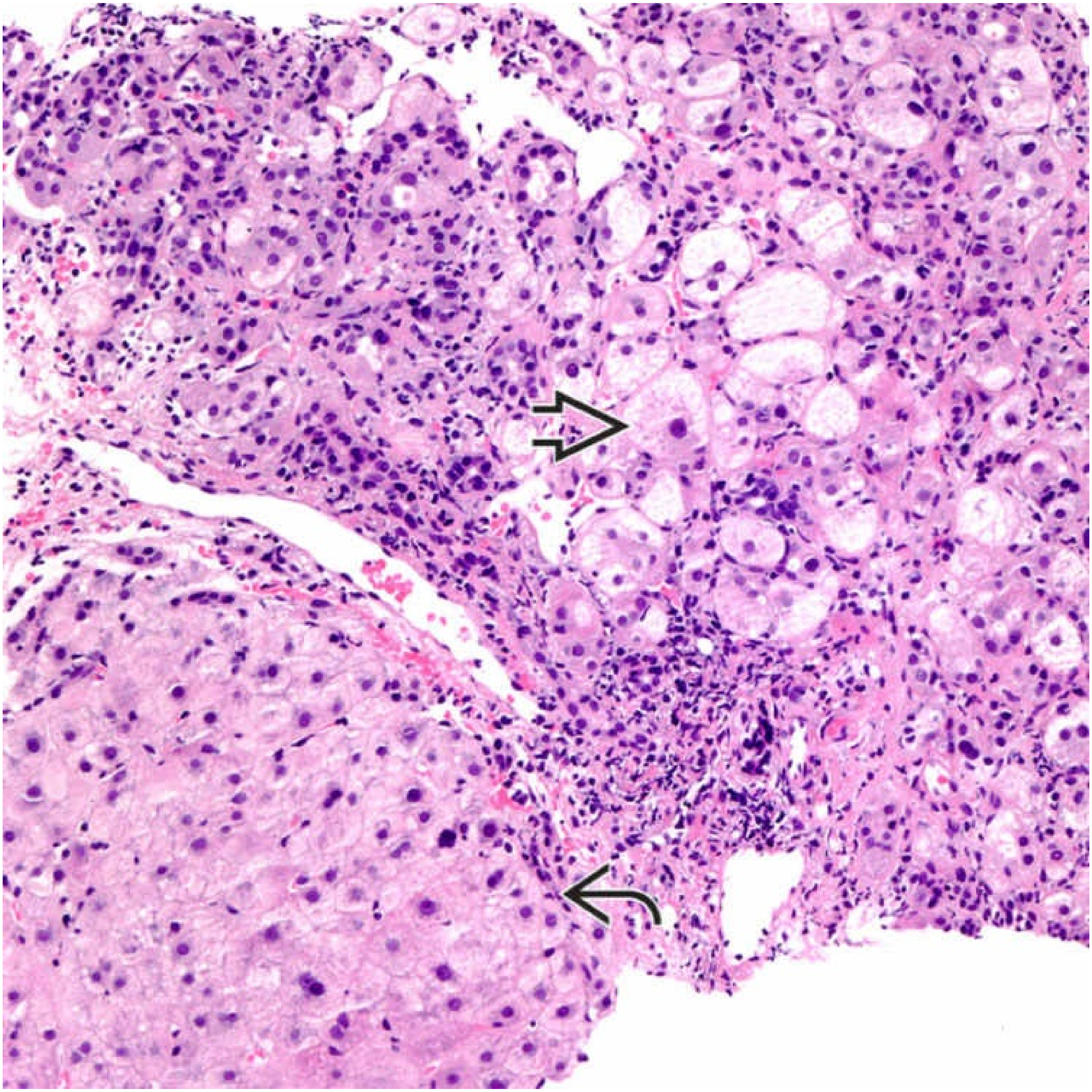


Steatosis

This higher power view from a Wilson disease biopsy shows mixed micro- and macrovesicular steatosis and glycogenated nuclei →, closely mimicking fatty liver disease of other etiologies.

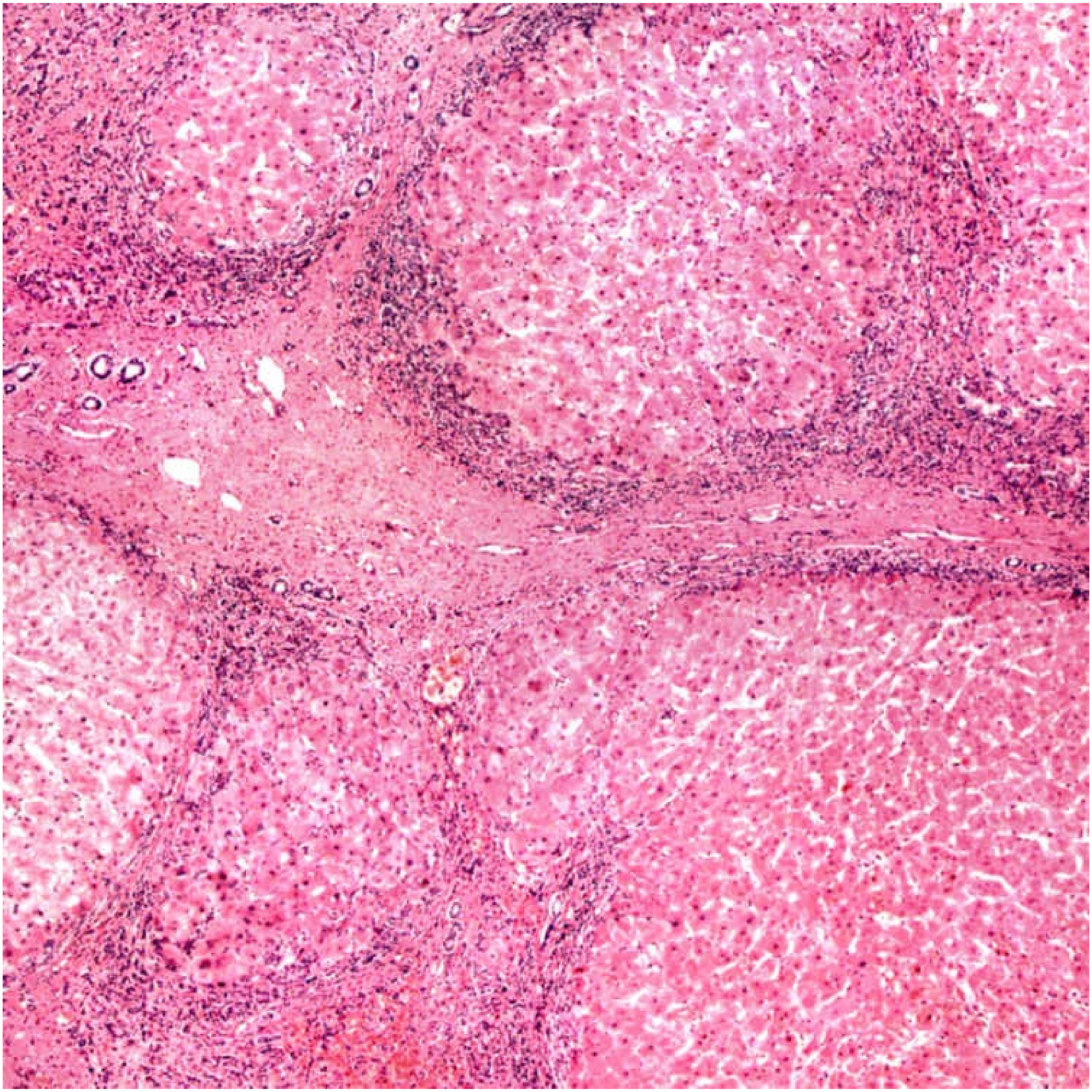


Apoptotic Hepatocytes
This Wilson disease biopsy shows portal and periportal chronic hepatitis with interface activity and apoptotic hepatocytes ➯ .

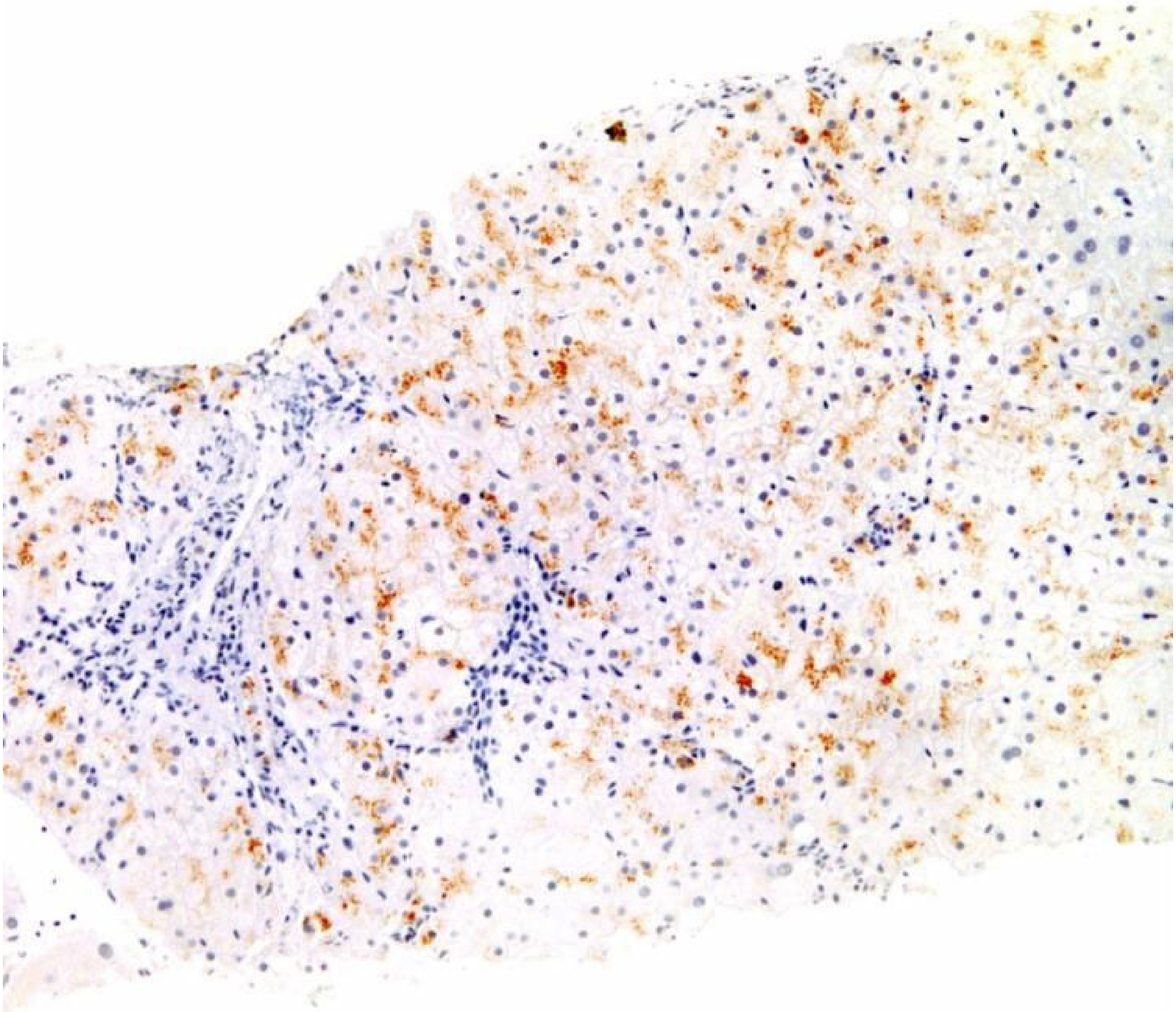


Ballooning Degeneration

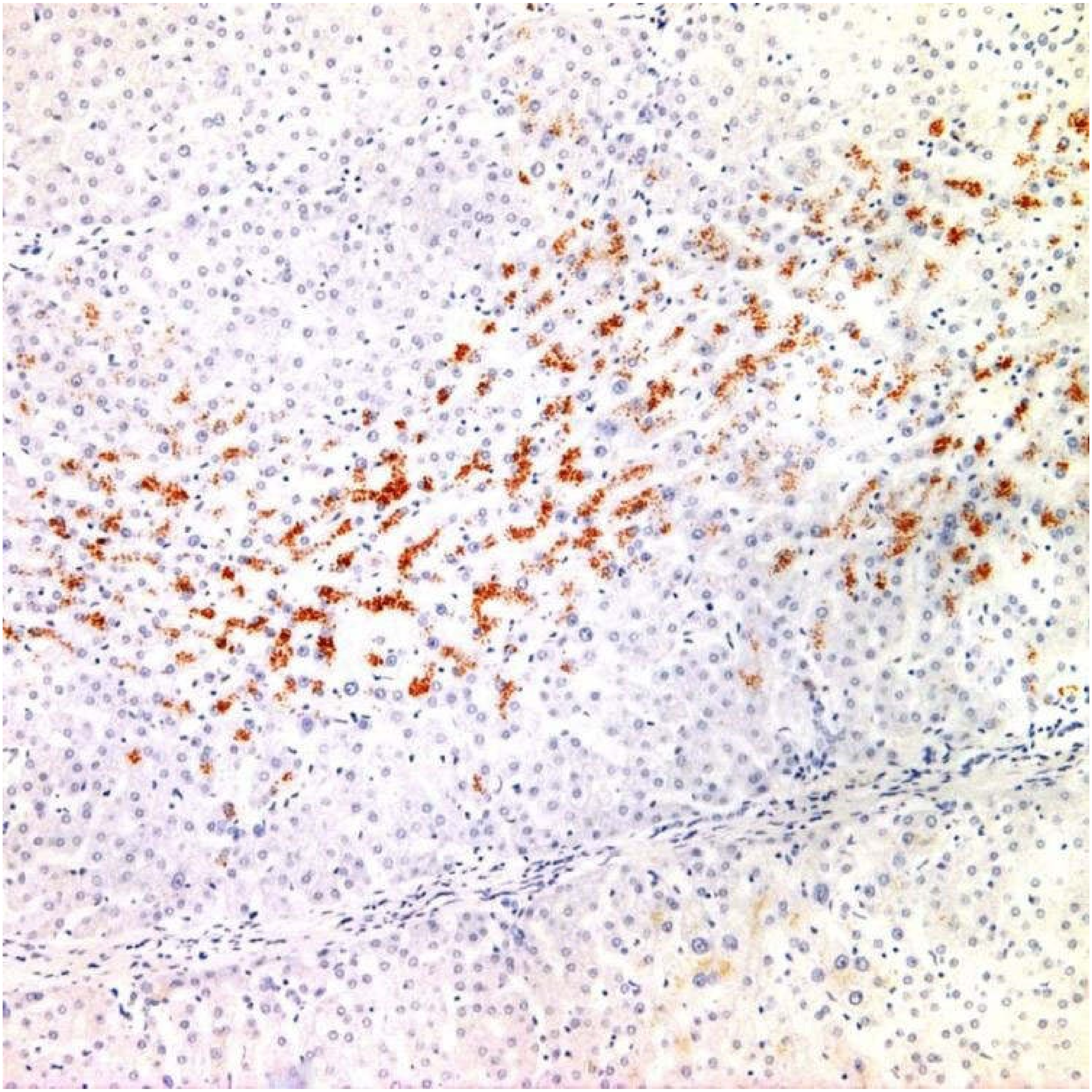
This case of Wilson disease demonstrates a more severe chronic hepatitis with active inflammation, ballooning degeneration of hepatocytes ⇨, and nodule formation ↷ .



Cirrhosis
This example of cirrhosis in Wilson disease shows well-developed cirrhotic nodules with chronic inflammatory infiltrates at the edges. Overall, the H&E features of cirrhosis in Wilson disease are nonspecific.

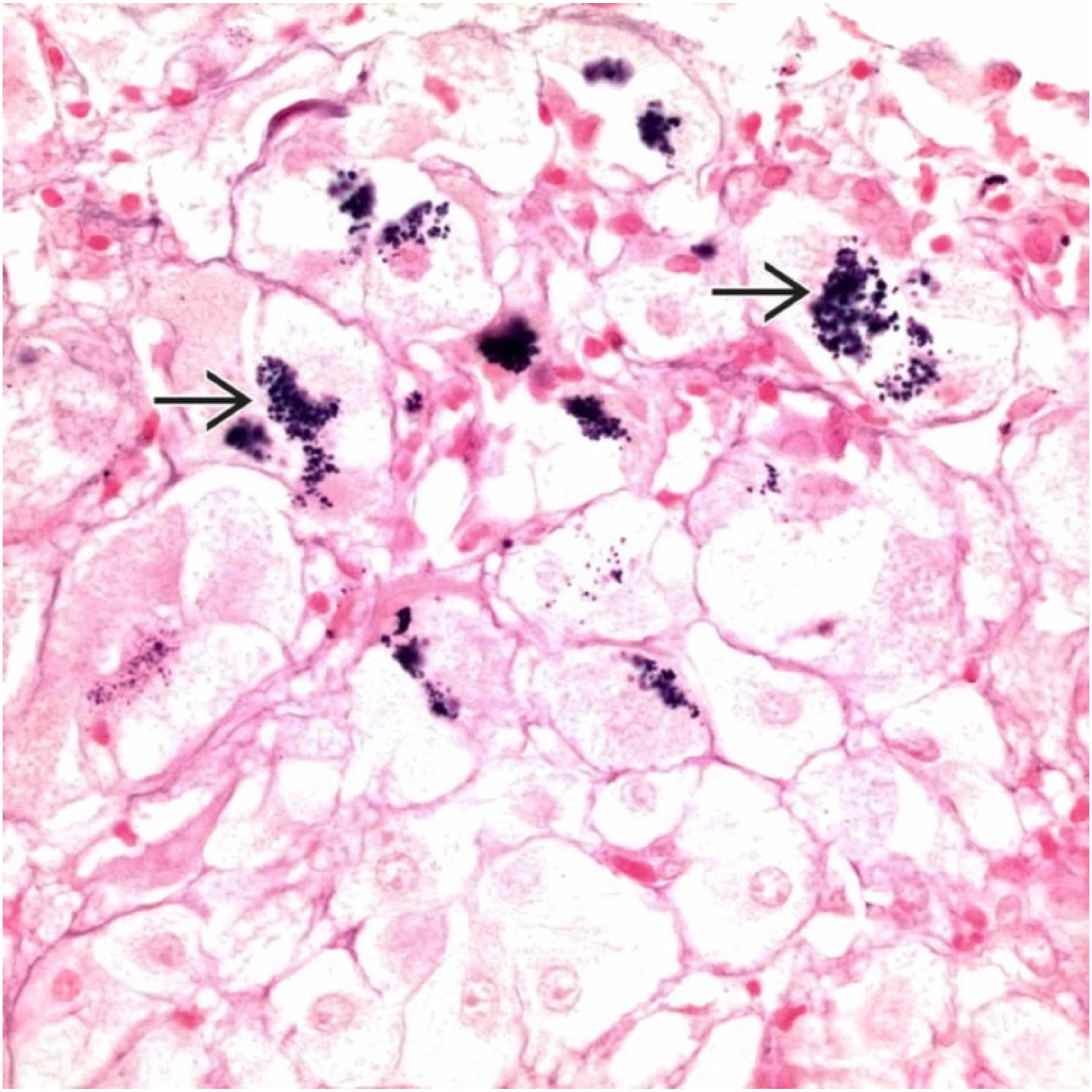


Copper Staining
The copper staining in Wilson disease is typically periportal early in the course of the disease but over time may extend to involve the entire lobule.



Copper Staining

This rhodanine stain at low power from a Wilson disease explant illustrates that copper staining may be focal or patchy; hence negative copper stain does not exclude disease.



Aldehyde Fuchsin
Aldehyde fuchsin stain shows darkly staining granules of copper-associated protein (metallothionein) in periportal hepatocytes →.

SELECTED REFERENCES

1. Ala, A, et al. Wilson's disease. *Lancet*. 2007; 369(9559):397–408.
2. Ala, A, et al. Wilson disease: pathophysiology, diagnosis, treatment, and screening. *Clin Liver Dis*. 2004; 8(4):787–805. [viii].
3. Gitlin, JD. Wilson disease. *Gastroenterology*. 2003; 125(6):1868–1877.
4. Gitlin, JD. Aceruloplasminemia. *Pediatr Res*. 1998; 44(3):271–276.
5. Davies, SE, et al. Hepatic morphology and histochemistry of Wilson's disease presenting as fulminant hepatic failure: a study of 11 cases. *Histopathology*. 1989; 15(4):385–394.

6. Sumithran, E, et al. Copper-binding protein in liver cells. *Hum Pathol*. 1985; 16(7):677–682.
7. Stromeyer, FW, et al. Histology of the liver in Wilson's disease: a study of 34 cases. *Am J Clin Pathol*. 1980; 73(1):12–24.

Alpha-1-Antitrypsin Deficiency

KEY FACTS

Terminology

- Genetic, autosomal recessive disorder characterized by abnormal α-1-antitrypsin (A1AT) protein synthesis
  - Caused by mutations in *SERPINA1* gene
- Deficiency is characterized by emphysema and chronic liver disease

Etiology/Pathogenesis

- Mutations result in defective secretion of molecule, accumulation in hepatocytes, and decreased serum A1AT
  - Specific mechanism of hepatocyte injury is unknown
- Most common deficiency alleles are PiS and PiZ
  - PiZZ phenotype accounts for most cases of severe A1AT deficiency and virtually all cases of liver disease

Clinical Issues

- Most common in Caucasians of Northern European ancestry
  - Liver disease is 2nd most common manifestation (after pulmonary disease)
  - Bimodal distribution
    - Neonatal hepatitis/cholestasis in infants
    - Chronic liver disease/cirrhosis in adults

Microscopic

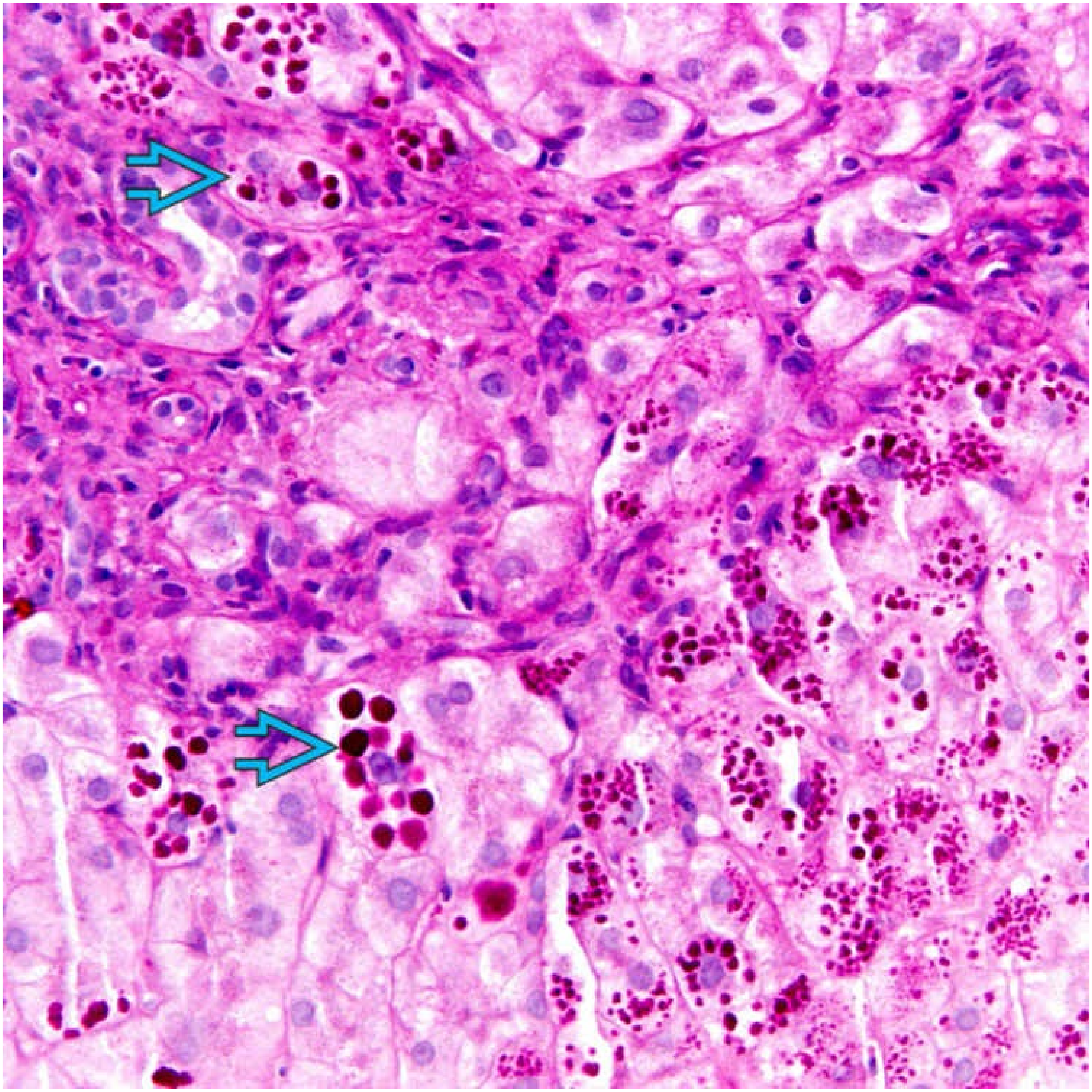
- Eosinophilic globules within periportal/periseptal hepatocytes are characteristic
  - Globules are strongly PAS(+), diastase resistant
  - Present in periportal/periseptal hepatocytes
  - Associated histologic features (inflammation, fibrosis) in adults are variable and nonspecific
- Neonatal hepatitis features cholestasis, hepatocyte injury
  - Globules may be difficult to detect in young infants

Diagnostic Checklist

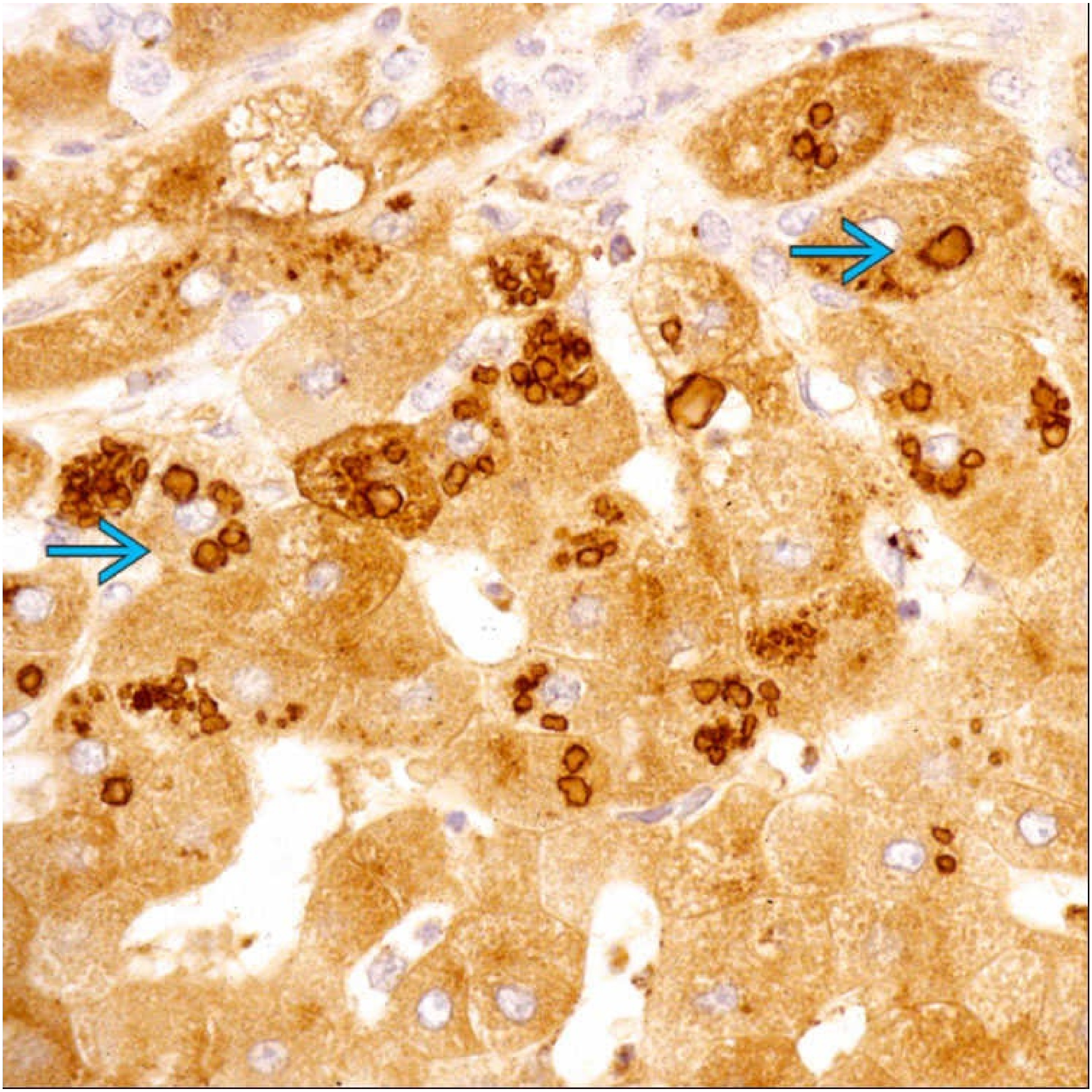
- Consider A1AT deficiency in all cases of neonatal cholestasis or in adults with unexplained chronic liver disease

Explanted Liver

Gross photograph of an explanted liver from an adult with an α-1-antitrypsin (A1AT) deficiency shows nodular capsular and cut surfaces consistent with cirrhosis. Cirrhosis is frequently established at the time of diagnosis in adults.

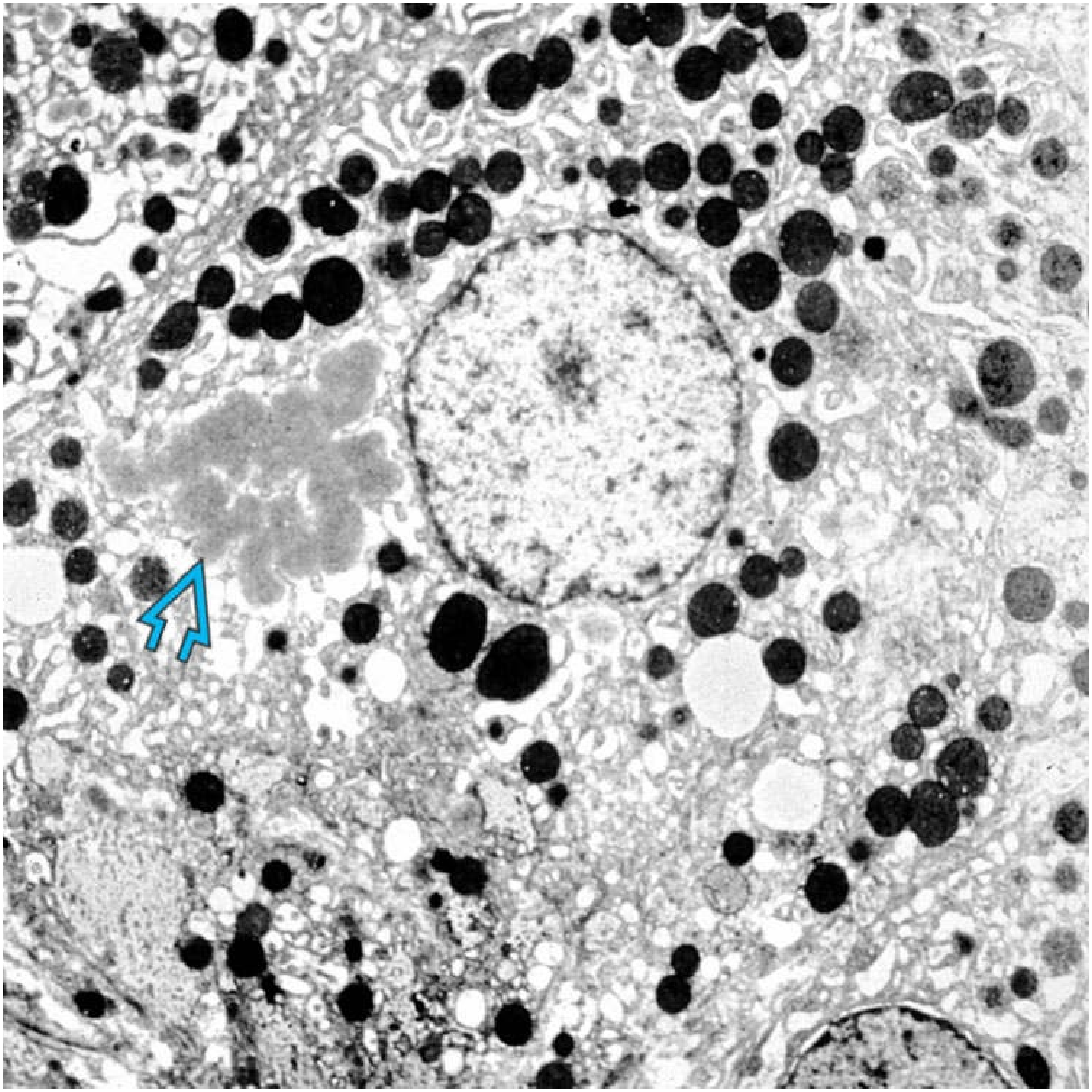


PAS-Diastase Stain
PAS with diastase digestion shows numerous periportal PAS(+) diastase-resistant globules in periportal areas.



α-1-Antitrypsin Stain

A1AT immunohistochemical stain confirms the presence of A1AT inclusion bodies within hepatocytes →. The peripheral pattern of staining of each globule is characteristic. In neonates, there is typically more granular cytoplasmic staining, as well-formed globules are not usually present in this age group.



Electron Micrograph
Electron micrograph shows round, electron-dense deposits within the endoplasmic reticulum of a hepatocyte .

TERMINOLOGY

Abbreviations

- α-1-antitrypsin (A1AT)

Definitions

- Autosomal recessive genetic disorder characterized by mutations in *SERPINA1* gene

○ A1AT protein synthesized mainly in liver
– Major circulating serine protease inhibitor
– Inhibits neutrophil proteases, thus protecting host tissues from nonspecific injury secondary to inflammation

○ Mutations result in defective secretion of molecule
– Most commonly Glu342Lys substitution
– Protein folds abnormally forming insoluble aggregates instead of being secreted

○ Deficiency is characterized by emphysema and chronic liver disease
• Most common inherited metabolic disorder leading to liver transplantation in childhood
• Most common genetic cause of liver disease in adults and children

ETIOLOGY/PATHOGENESIS

Inherited Metabolic Disorder

• Highly polymorphic genes with many recognized variants
○ Variants comprise protease inhibitor (Pi) system
– Most common variant is PiM
□ Present in > 90% of USA population
□ Associated with normal serum A1AT levels
– Most common deficiency alleles are PiS and PiZ
□ PiZZ phenotype accounts for most cases of severe A1AT deficiency
□ ~ 0.5% of population
□ Typically Caucasians of Northern European ethnicity
– ~ 2% of individuals are heterozygous for Z allele
□ Risk of liver disease in heterozygotes is controversial

Accumulation of Mutant Protein

• Coding sequence defects lead to abnormal polymerization of glycoprotein, preventing export from hepatocyte
○ Mutant protein accumulates in endoplasmic reticulum of hepatocyte
– Subsequent decrease in serum A1AT
– Specific mechanism of hepatocyte injury is unknown

CLINICAL ISSUES

Epidemiology

• Incidence

- Severe A1AT deficiency is found in ~ 1 per 3,500 live births
- Age
  - Bimodal distribution: Hepatitis and cholestesis in neonates, chronic liver disease in adults
    - ~ 2% of A1AT-deficient persons between the ages of 20-40 develop liver disease; increases thereafter
- Sex
  - No predilection until age 50, then male predominance
- Ethnicity
  - Most common in Caucasians of Northern European ancestry

Presentation

- Pulmonary emphysema
  - Often early in adulthood
  - Particularly in smokers but also in nonsmokers

- Most common manifestation of disease

- Liver disease
  - Less common manifestation than pulmonary disease
    - Development of clinically significant liver disease in A1AT deficient patients is highly variable
      - Male gender and obesity associated with more severe liver disease
  - Almost always associated with PiZZ phenotype
  - Adults
    - Variable presentation, ranging from asymptomatic elevation of liver enzymes to cirrhosis
    - Risk of cirrhosis appears to increase with age
    - Patients have increased risk of both hepatocellular carcinoma and cholangiocarcinoma
  - Neonates
    - Neonatal hepatitis/cholestasis is most common liver presentation (5-10% of infants with neonatal cholestasis)
      - Majority of PiZZ infants have abnormal liver tests
      - 10-20% develop overt liver disease with jaundice, hepatomegaly, acholic stools
- Risks of developing lung and liver disease in A1AT deficient patients appear to be independent
  - Presence of one manifestation does not exclude possibility of developing other

Laboratory Tests

- Serum levels of A1AT < 35% of normal
  - A1AT is acute-phase reactant, thus may be elevated secondary to inflammation, causing normal levels in heterozygotes
- Pi phenotyping by polyacrylamide gel isoelectric focusing
- DNA sequencing

Treatment

- Liver transplantation
  - Patients assume donor phenotype and revert to normal serum levels of A1AT

- A1AT augmentation therapy and gene therapy are active areas of investigation

Prognosis

- Children
  - ∼ 25% spontaneously regress by 6 months of age
  - ∼ 1/2 have persistent biochemical abnormalities, jaundice, &/or hepatomegaly
  - Minority (20-30%) develop cirrhosis &/or liver failure
- Adults
  - Poor prognosis after diagnosis of cirrhosis
  - Small but definite increased risk of hepatocellular carcinoma
    - Patients with cirrhosis secondary to A1AT deficiency should be screened for hepatocellular carcinoma

MACROSCOPIC

General Features

- Hepatomegaly, cirrhosis

MICROSCOPIC

Histologic Features

- Characteristic feature is abnormal hepatocellular inclusions
  - Eosinophilic round globules
  - Strongly PAS(+), diastase resistant
  - Variable size (1-40 μm in diameter)
  - Represent accumulations of abnormal A1AT in endoplasmic reticulum
- Most prominent in periportal/periseptal hepatocytes
- Seen in heterozygous (PiMZ, PiSZ) as well as homozygous individuals (PiZZ)
- Globules are essentially markers of Z allele
- Histologic features very variable in adults
  - Variably present portal inflammation
    - Predominance of lymphocytes
  - Steatosis, mild cholestasis variably present as well
  - Cirrhosis often present at diagnosis
    - Nonspecific mixed micronodular and macronodular pattern
  - Significant association between H63D mutation for hemochromatosis and cirrhosis secondary to A1AT deficiency
    - Livers explanted for A1AT often show increased iron
- Neonatal presentation

  - Varying degree of hepatocyte injury (ballooning and necrosis)
    - Giant cell change may be present as well
  - Cholestasis
    - Hepatocellular and canalicular
  - Portal inflammation
  - Globules are difficult to detect in infants < 12 weeks of age
    - May see more nonspecific granules rather than well-formed globules
  - Fibrosis typically mild
- Some cases of A1AT deficiency show paucity of intrahepatic bile ducts

ANCILLARY TESTS

Immunohistochemistry

- A1AT immunostain can be used to highlight globules
  - Background staining is often high, thus stain may be difficult to interpret

DIFFERENTIAL DIAGNOSIS

Lafora Disease

- Inclusions are pale and round or kidney-shaped; displace nuclei
  - Stain with with colloidal iron and silver stains
- Patients have severe neurological manifestations

Fibrinogen Storage Disease

- Pale, weakly eosinophilic, PAS(-) ground-glass bodies
- Immunohistochemical stain for fibrinogen strongly positive

Congestion-Associated Globules

- Centrilobular distribution of PAS(+), diastase-resistant globules rather than periportal/periseptal distribution
- Associated with sinusoidal congestion and hepatic hypoxia

Extrahepatic Biliary Atresia

- Abnormal imaging studies
  - Notably, however, biliary imaging studies in A1AT deficiency may be abnormal
- Normal serum A1AT levels

Other Causes of Neonatal Hepatitis

- Typically infectious (e.g., CMV, HSV, rubella)

- Normal serum A1AT levels
- Lack abnormal A1AT inclusions, although this may be difficult to evaluate in very young infants

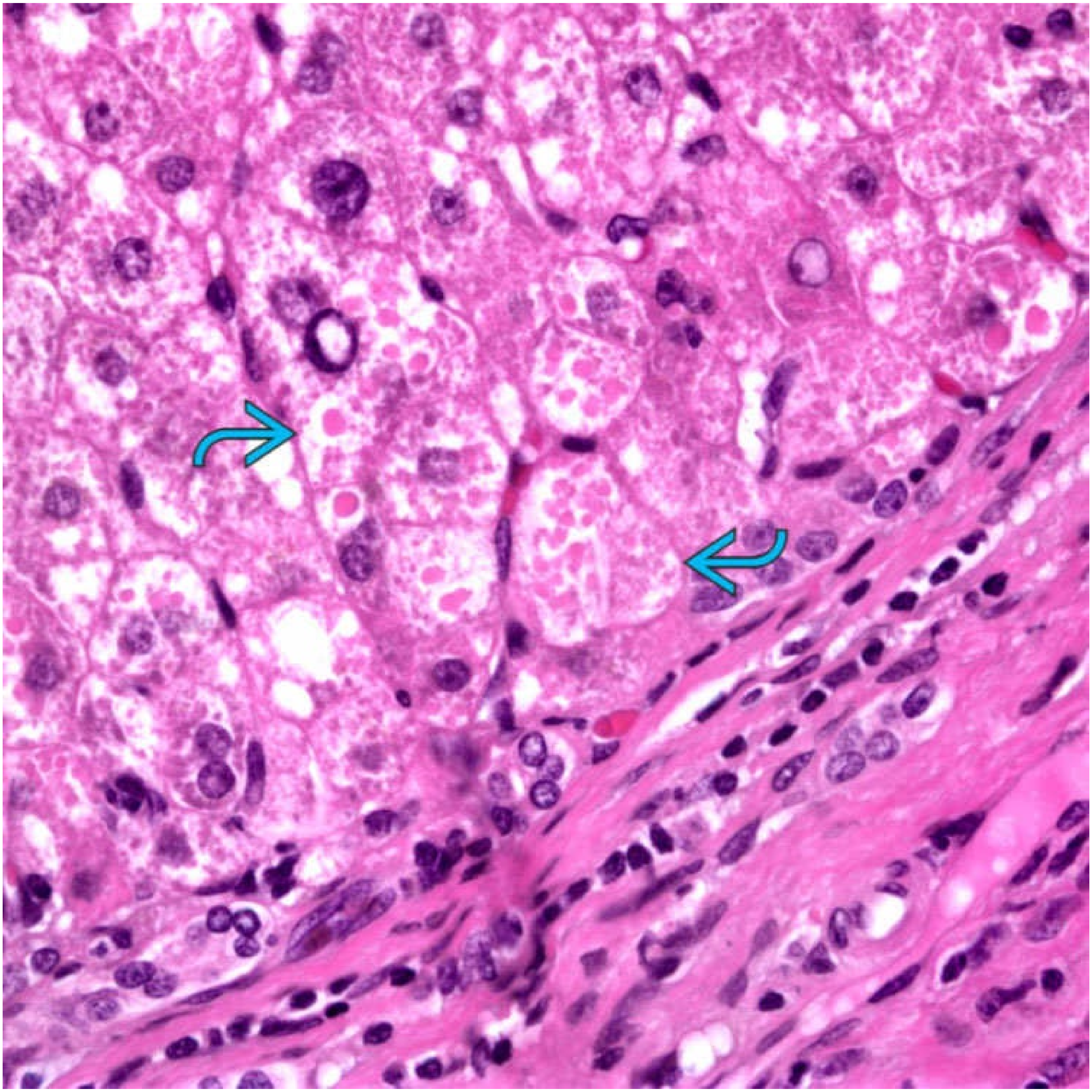
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Consider A1AT deficiency
  - In all cases of neonatal cholestasis
  - In adults with unexplained chronic liver disease
- Serum A1AT levels may be normal secondary to inflammation

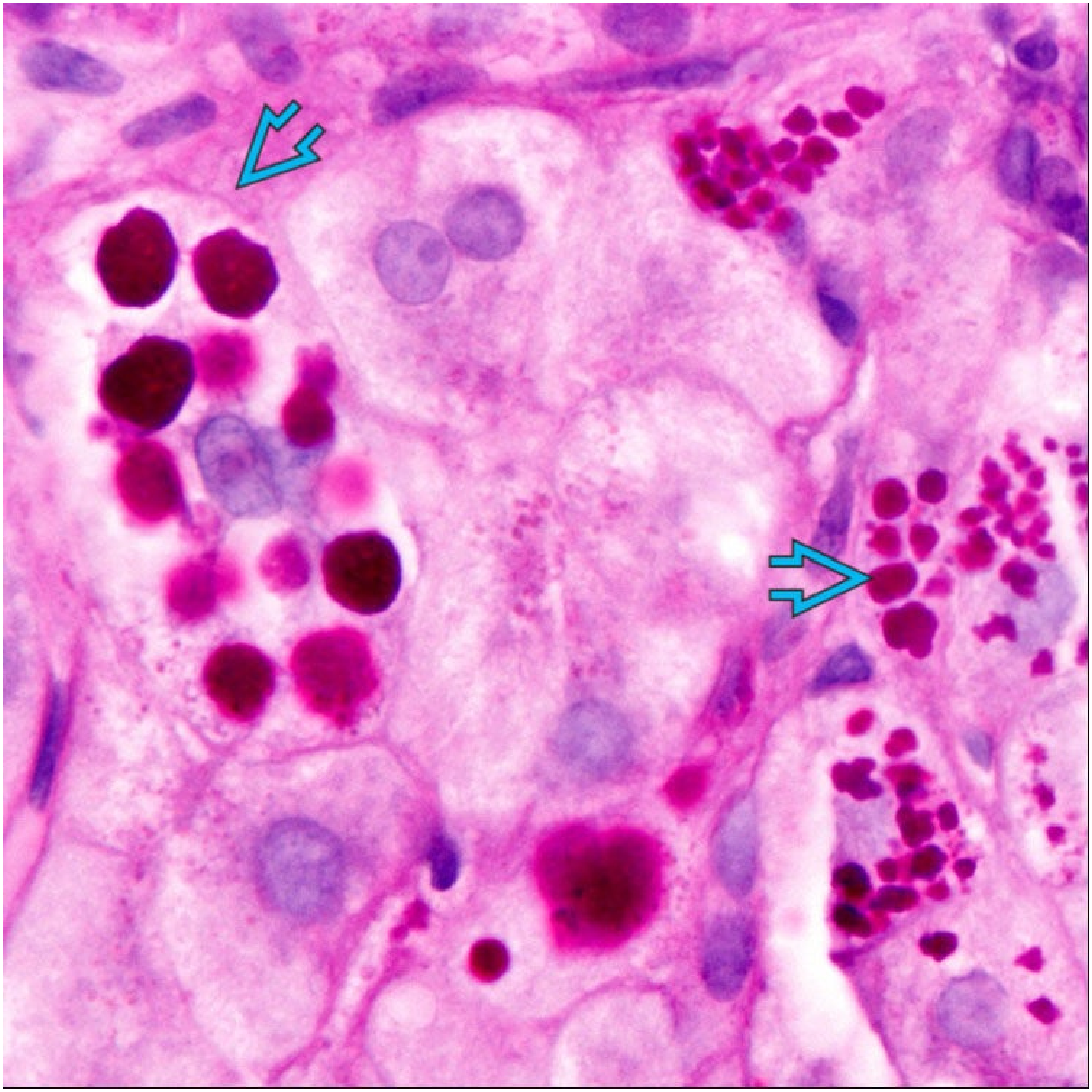
Pathologic Interpretation Pearls

- PAS(+), diastase-resistant, eosinophilic globules in periportal/periseptal distribution



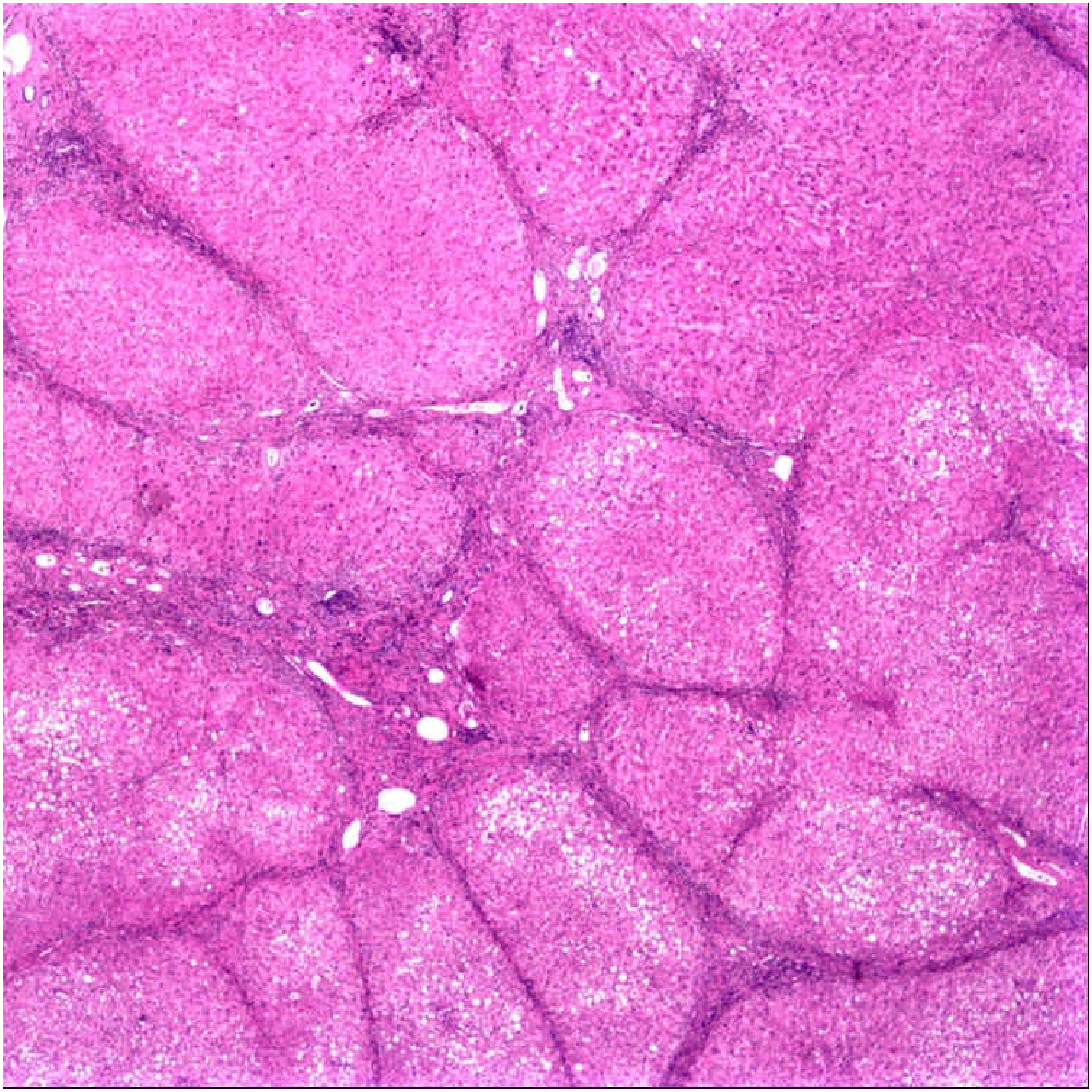
Eosinophilic Globules

This section shows numerous eosinophilic globules within the cytoplasm of periportal hepatocytes. The globules are often visible on H&E sections.

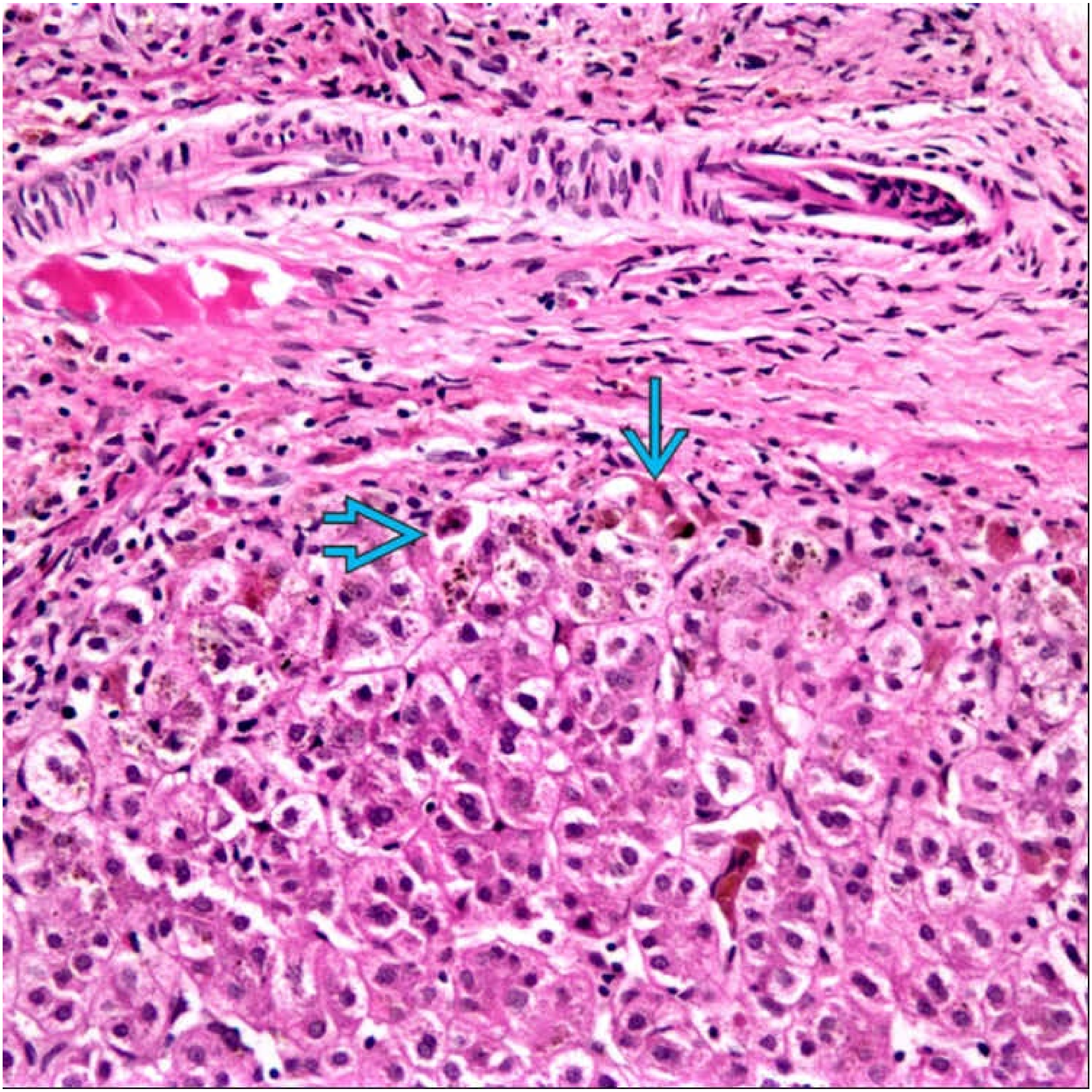


Globules: PAS With Diastase

PAS with diastase digestion shows round, homogeneous, intracytoplasmic inclusions ➡ of varying sizes that are strongly PAS(+) and diastase resistant. This feature is typical of A1AT deficiency.

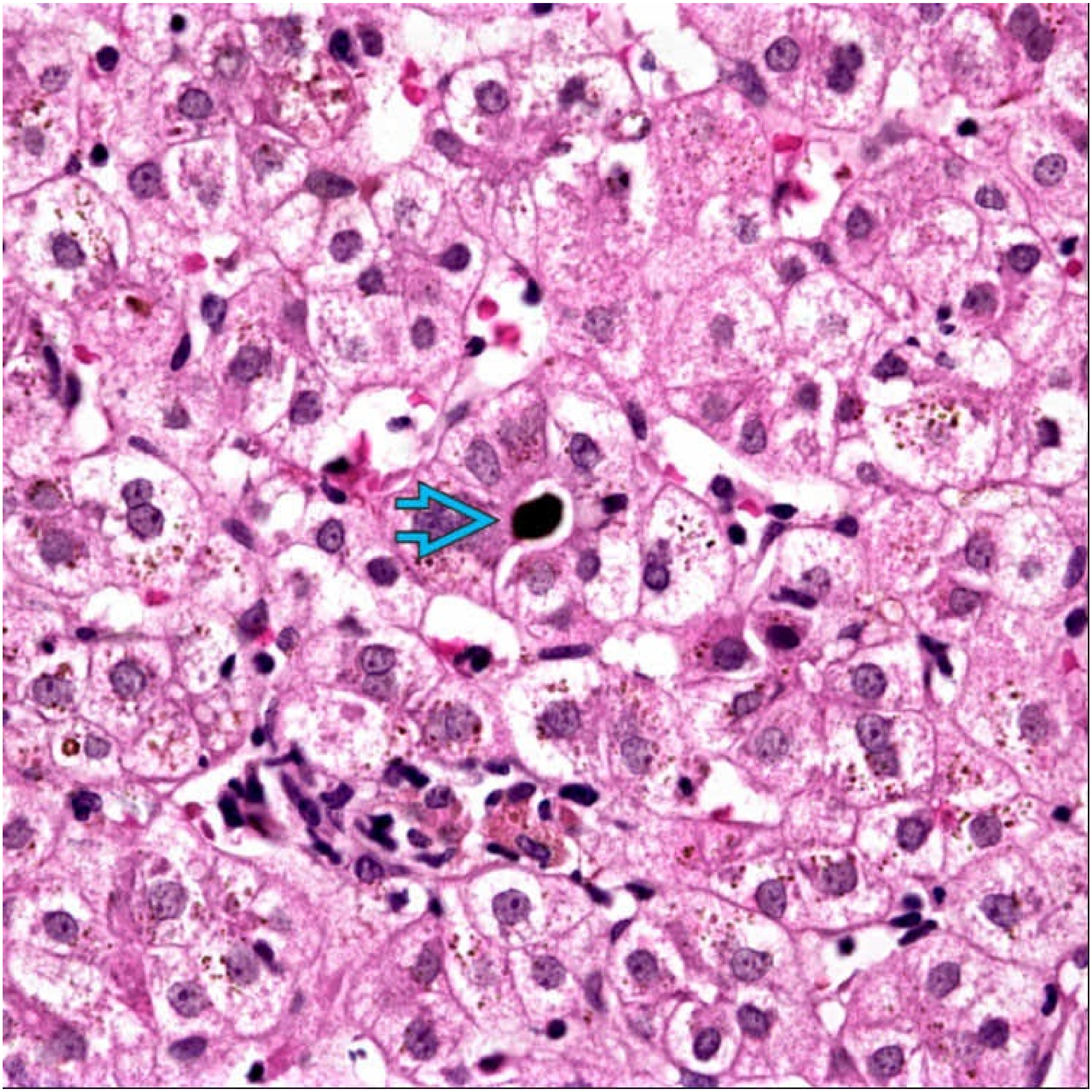


Cirrhosis
H&E section shows cirrhosis and mild steatosis. The pattern of cirrhosis in A1AT deficiency is nonspecific and may consist of nodules of varying sizes and shapes.

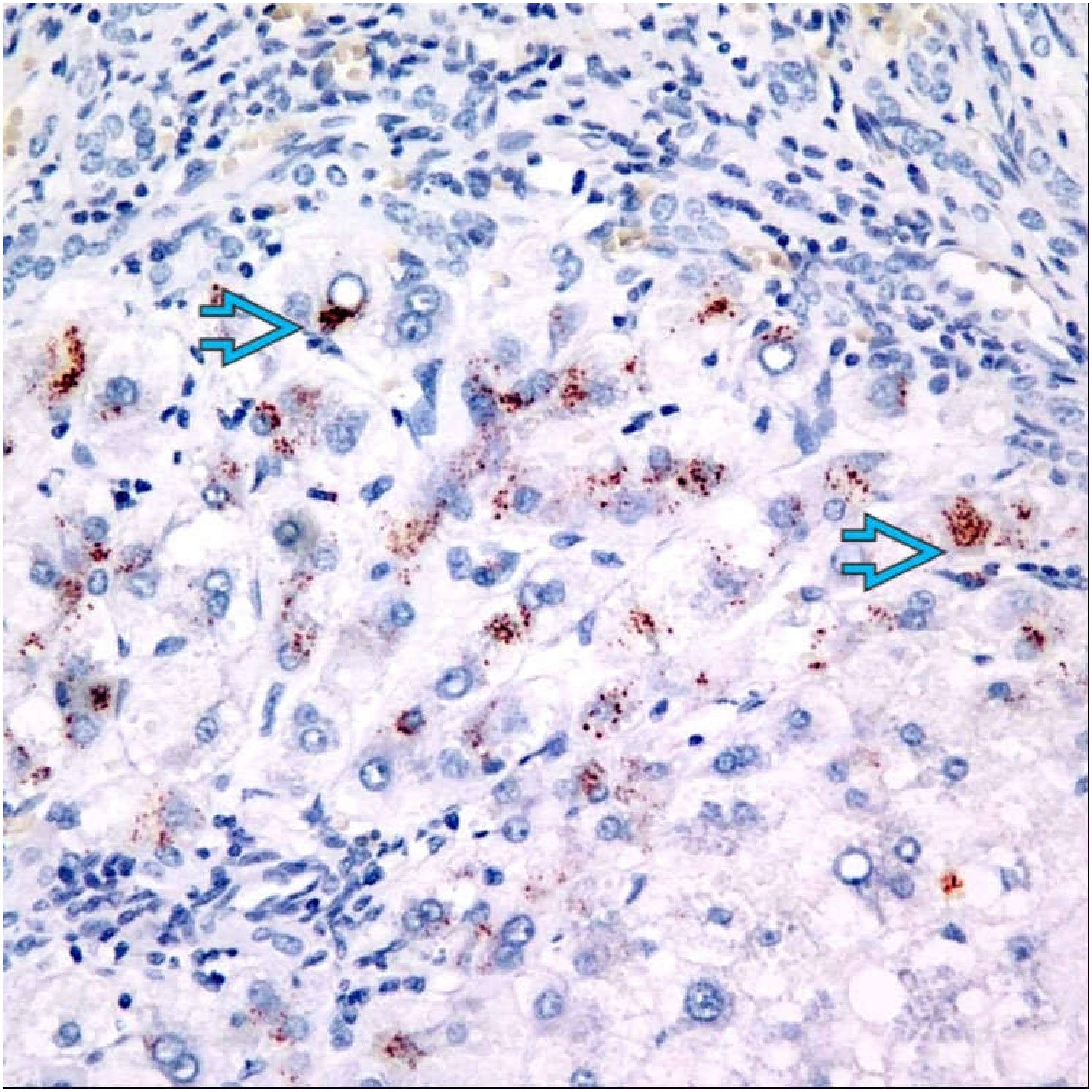


Neonatal A1AT Deficiency

Neonates with A1AT deficiency often present with cholestasis. This biopsy shows marked cholestasis →, predominantly in a periportal distribution, with hepatocyte ballooning and focal hepatocyte necrosis ⇨. The amount of portal tract inflammation is variable; in this case, there is minimal portal tract inflammation.



Neonatal A1AT Deficiency
Neonatal A1AT deficiency at higher magnification shows hepatocyte ballooning, along with a cholestatic rosette containing a bile plug .



Copper Stain, Neonatal A1AT Deficiency

Copper stain highlights red-brown granules within periportal hepatocytes ➩ consistent with cholate stasis (chronic cholestasis). This feature is frequently seen in neonates who present with cholestatic hepatitis secondary to A1AT deficiency and in adults with cirrhosis.

SELECTED REFERENCES

1. Carey, EJ, et al. Outcomes for recipients of liver transplantation for alpha-1-antitrypsin deficiency–related cirrhosis. *Liver Transpl*. 2013; 19(12):1370–1376.
2. Sabina, J, et al. Augmentation therapy with alpha1-antitrypsin: novel perspectives. *Cardiovasc Hematol Disord Drug Targets*. 2013; 13(2):90–98.
3. Nelson, DR, et al. Diagnosis and management of patients with α1-antitrypsin (A1AT) deficiency. *Clin Gastroenterol Hepatol*. 2012; 10(6):575–580.

4. Lam, M, et al. HFE mutations in alpha-1-antitrypsin deficiency: an examination of cirrhotic explants. *Mod Pathol*. 2010; 23(5):637–643.
5. Fairbanks, KD, et al. Liver disease in alpha 1-antitrypsin deficiency: a review. *Am J Gastroenterol*. 2008; 103(8):2136–2141. [quiz 2142].
6. Stoller, JK, et al. Alpha1-antitrypsin deficiency. *Lancet*. 2005; 365(9478):2225–2236.
7. Eriksson, S. Alpha 1-antitrypsin deficiency. *J Hepatol*. 1999; 30(Suppl 1):34–39.
8. Birrer, P, et al. Alpha 1-antitrypsin deficiency and liver disease. *J Inherit Metab Dis*. 1991; 14(4):512–525.

Congenital Hepatic Fibrosis

KEY FACTS

Terminology

- Variant of ductal plate malformation that leads to portal and bridging fibrosis, proliferation of aberrant duct profiles, and portal hypertension

Etiology/Pathogenesis

- Ductal plate malformation at level of interlobular bile ducts
- Persistence of excess embryonic bile ducts
- Primarily autosomal recessive inheritance, rarely autosomal dominant
- Frequent association with autosomal recessive polycystic kidney disease and Caroli syndrome

Clinical Issues

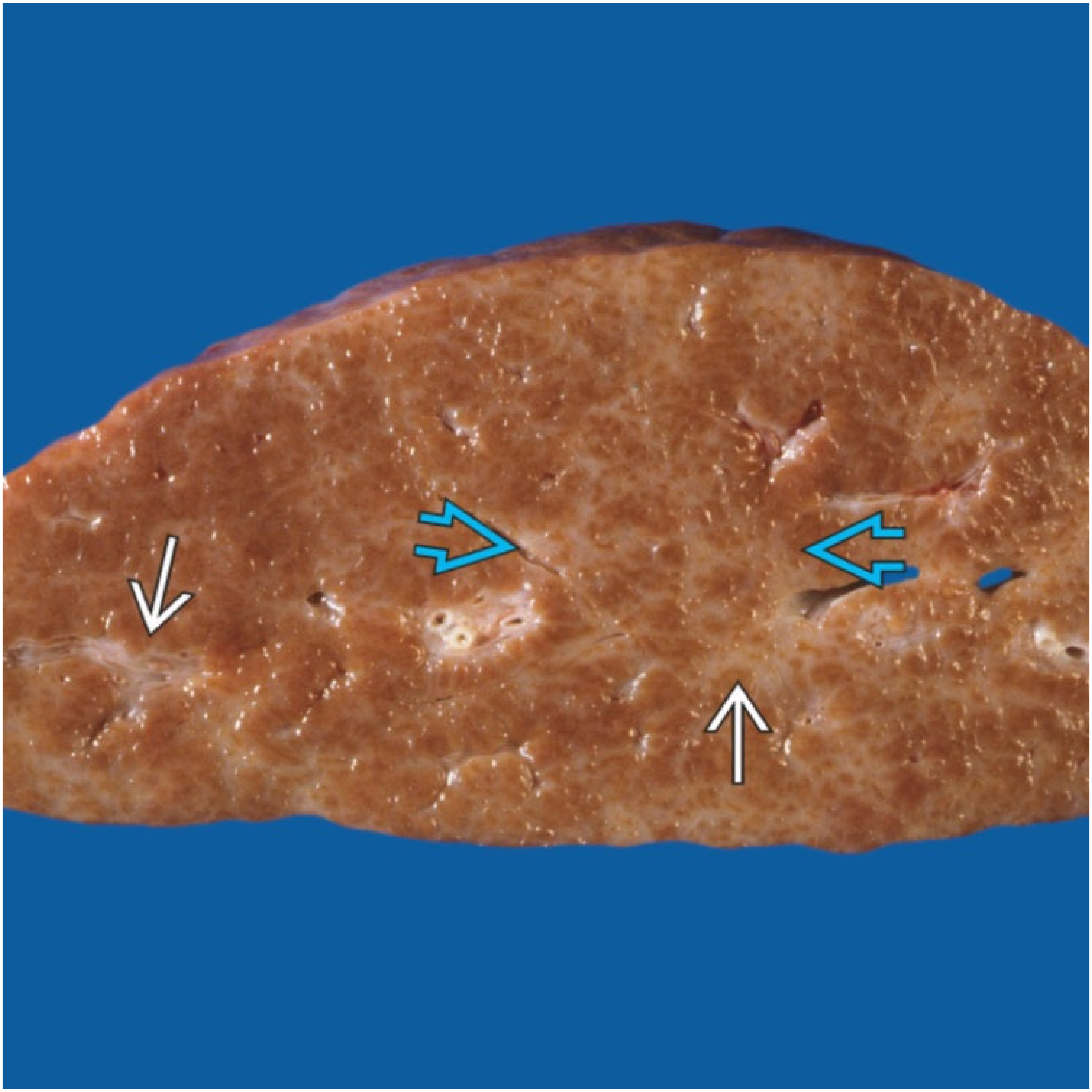
- Usually diagnosed during adolescence or young adulthood, but at much younger age when associated with polycystic kidney disease
  - Portal hypertension
  - Generally good prognosis but can be debilitating
  - Depending on severity of portal hypertension, biliary infection, and renal disease

Microscopic

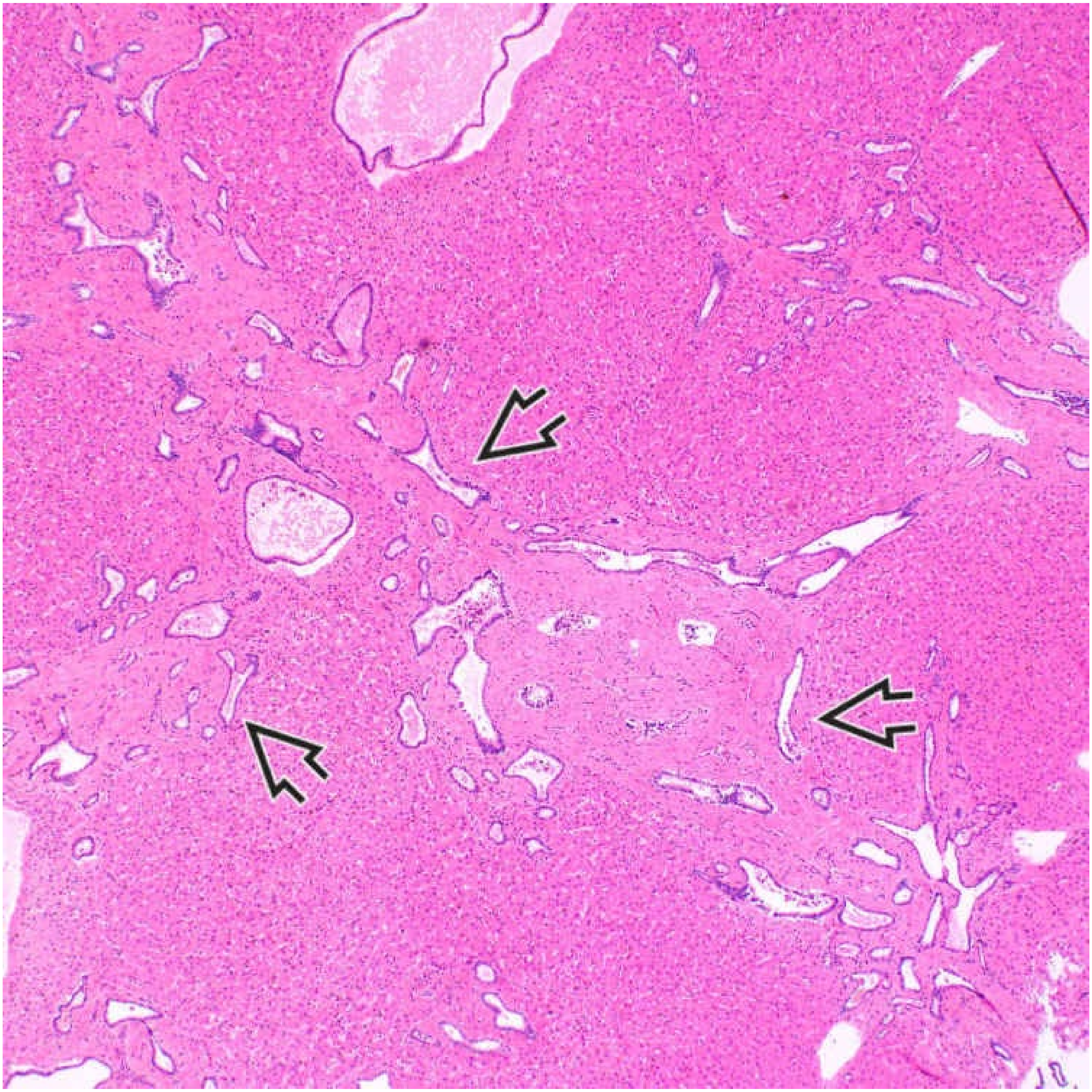
- Marked portal expansion by fibrous tissue
  - Portal-to-portal bridging fibrosis with broad septa
- Increased number of irregularly shaped, ectatic, branching, and anastomosing bile ducts
  - Sometimes line border of portal tracts or fibrous septa in ductal plate configuration
  - Inspissated bile may be seen in lumina of ducts
- Portal vein branches may be hypoplastic or reduced in number, or show cavernous transformation
- Hepatic artery branches may be hypertrophic or abnormally numerous

Top Differential Diagnoses

• Cirrhosis
• von Meyenburg complexes

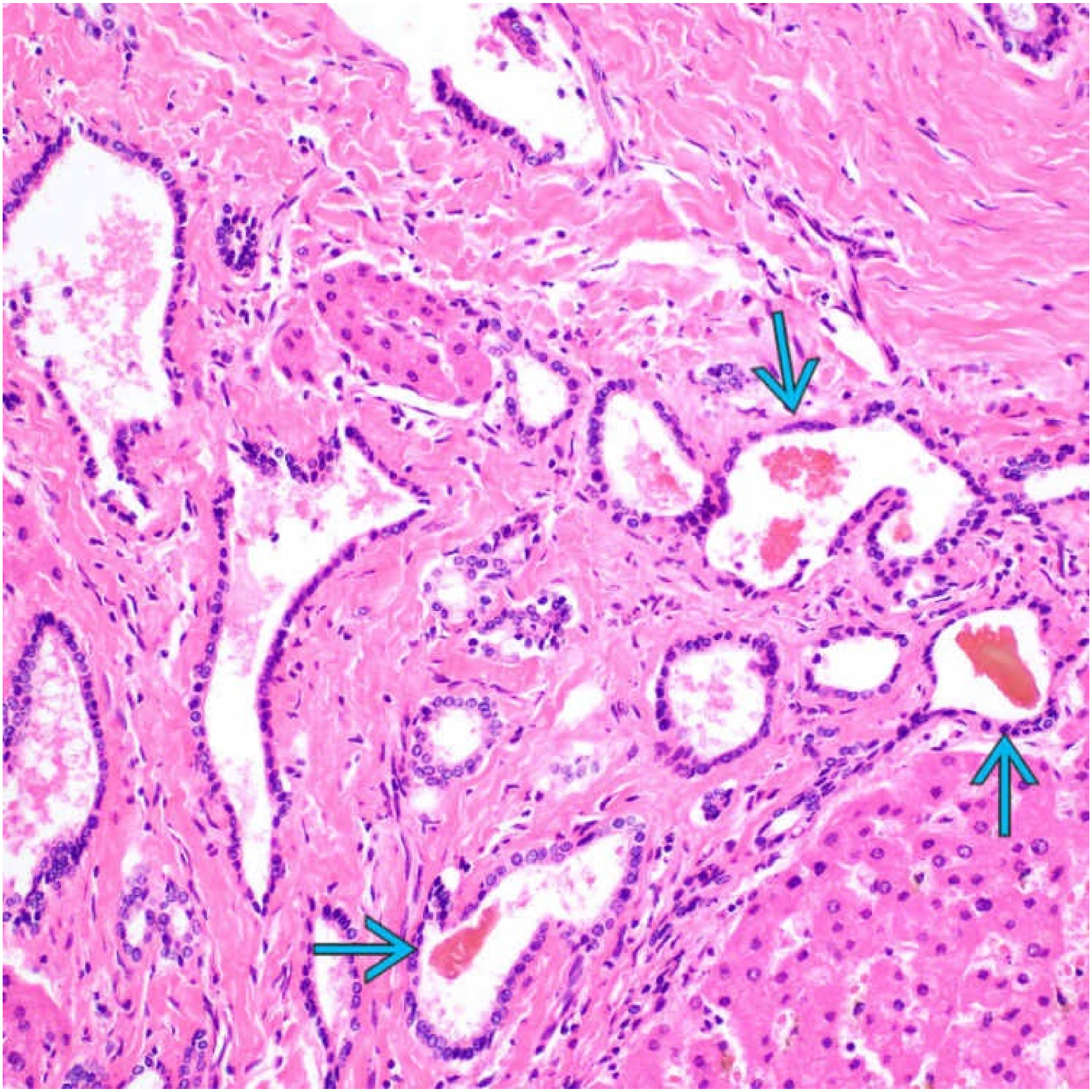


Gross Appearance
A gross photograph of congenital hepatic fibrosis shows white fibrous bands ⇒ that divide the liver parenchyma in a reticular pattern ⇒. There is no definite nodularity, as opposed to cirrhosis.

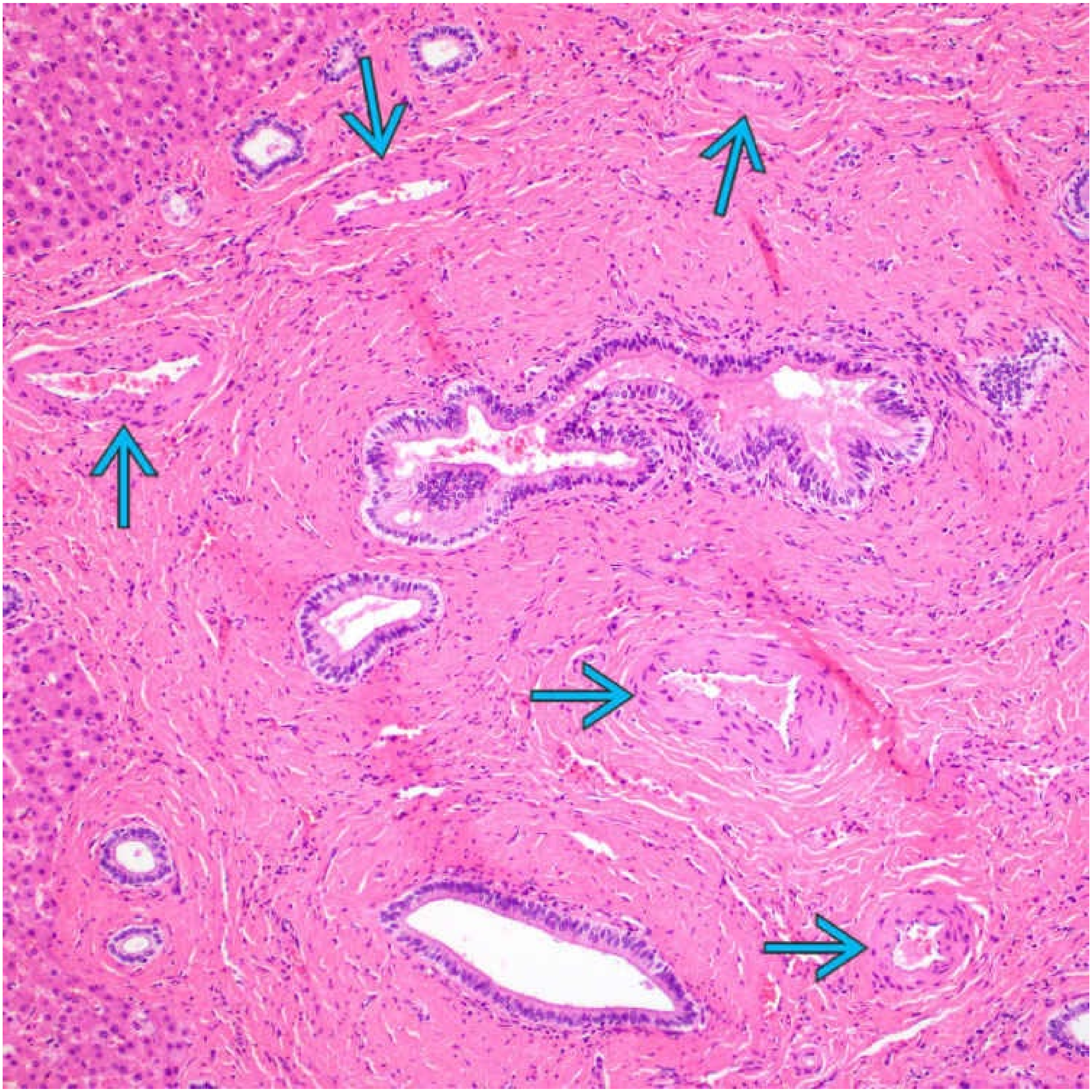


Bridging Fibrosis and Aberrant Ducts

Marked fibrous portal expansion with bridging fibrosis and numerous ectatic and irregularly shaped bile ducts are present, some of which are characteristically located at the interface with liver parenchyma ➩.
Note that there is no significant inflammation in this case.



Inspissated Bile
The aberrantly formed bile ducts are lined by cuboidal biliary epithelium, and some contain inspissated bile →. There is no significant inflammation.



Vascular Anomalies
Portal vein branches may be hypoplastic or reduced in number. This fibrotic portal tract contains multiple prominent hepatic artery branches →, but portal veins are not recognizable.

TERMINOLOGY

Abbreviations

- Congenital hepatic fibrosis (CHF)

Definitions

- Variant of ductal plate malformation that leads to portal and bridging fibrosis, proliferation of aberrant

duct profiles, and portal hypertension

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Ductal plate malformation at level of interlobular bile ducts
- Persistence of excess embryonic bile ducts
- Primarily autosomal recessive inheritance, rarely autosomal dominant

Disease Associations

- Autosomal recessive polycystic kidney disease
  - Most common coexisting condition
  - Affecting 1 in 20,000 live births
  - Mutations in *PKHD1* gene encoding fibrocystin/polyductin located in primary cilia
  - – Most common ciliopathy of childhood
- Autosomal dominant polycystic kidney disease
- Caroli disease (Caroli syndrome)
- Congenital disorder of glycosylation type 1b
- Meckel-Gruber syndrome
- Joubert syndrome and related disorders, including COACH syndrome
- Bardet-Biedl syndrome
- Jeune syndrome
- Oral-facial-digital syndrome

CLINICAL ISSUES

Epidemiology

- Incidence
  - Unknown, but uncommon
- Age
  - Birth to 75 years
    - Usually diagnosed during adolescence or young adulthood, but at much younger age when associated with polycystic kidney disease

Presentation

- Portal hypertension and related problems
- Hepatosplenomegaly
- Recurrent cholangitis if it presents as Caroli syndrome
- Rare cases are asymptomatic

Laboratory Tests

- Normal or modestly elevated liver tests
- Thrombocytopenia in patients with splenomegaly

Treatment

- Directed at management of complications of portal hypertension
  - Endoscopic banding or sclerotherapy for varices
  - Transjugular intrahepatic portosystemic shunts
- Antibiotics for cholangitis
- Liver transplantation

Prognosis

- Generally good but can be debilitating
  - Depends on severity of portal hypertension, biliary infection, and renal disease
- Occasional evolution into true cirrhosis
- Rare occurrence of cholangiocarcinoma in adulthood

IMAGING

General Features

- Hypertrophic left and caudate lobes
- Increased echogenicity on ultrasound
- Periportal cuffing indicative of fibrosis on CT

MACROSCOPIC

General Features

- Enlarged and firm liver, but may be of normal size
- Irregular or reticular white fibrous bands dividing liver parenchyma
- No definite nodule formation

MICROSCOPIC

Histologic Features

- Marked portal expansion by fibrous tissue
  - Portal-to-portal bridging fibrosis with broad septa
  - Separation of hepatic parenchyma into irregularly shaped islands or nodules
    - Lack of nodular regeneration of hepatocytes
- Increased number of irregularly shaped, ectatic, branching, and anastomosing bile ducts
  - Sometimes line border of portal tracts or fibrous septa in ductal plate configuration
  - Inspissated bile may be seen in lumina of ducts that are lined by cuboidal to low columnar epithelium

- Portal vein branches may be hypoplastic or reduced in number, or show cavernous transformation
- Hepatic artery branches may be hypertrophic or abnormally numerous
- Lack of inflammation in portal tracts or fibrous septa unless associated with cholangitis

DIFFERENTIAL DIAGNOSIS

Cirrhosis

- Diffuse nodular regeneration of hepatocytes and remodeling of hepatic architecture
- Varying degrees of inflammation
- Compromised liver function
- No association with polycystic kidney disease

Idiopathic Portal Hypertension

- Lack of bridging fibrosis
- Lack of abnormally proliferative bile ducts
- Characterized by narrowing or obliteration of portal vein branches

von Meyenburg Complexes

- No portal hypertension
- Typically small nodular lesions that are incidental findings in otherwise normal liver

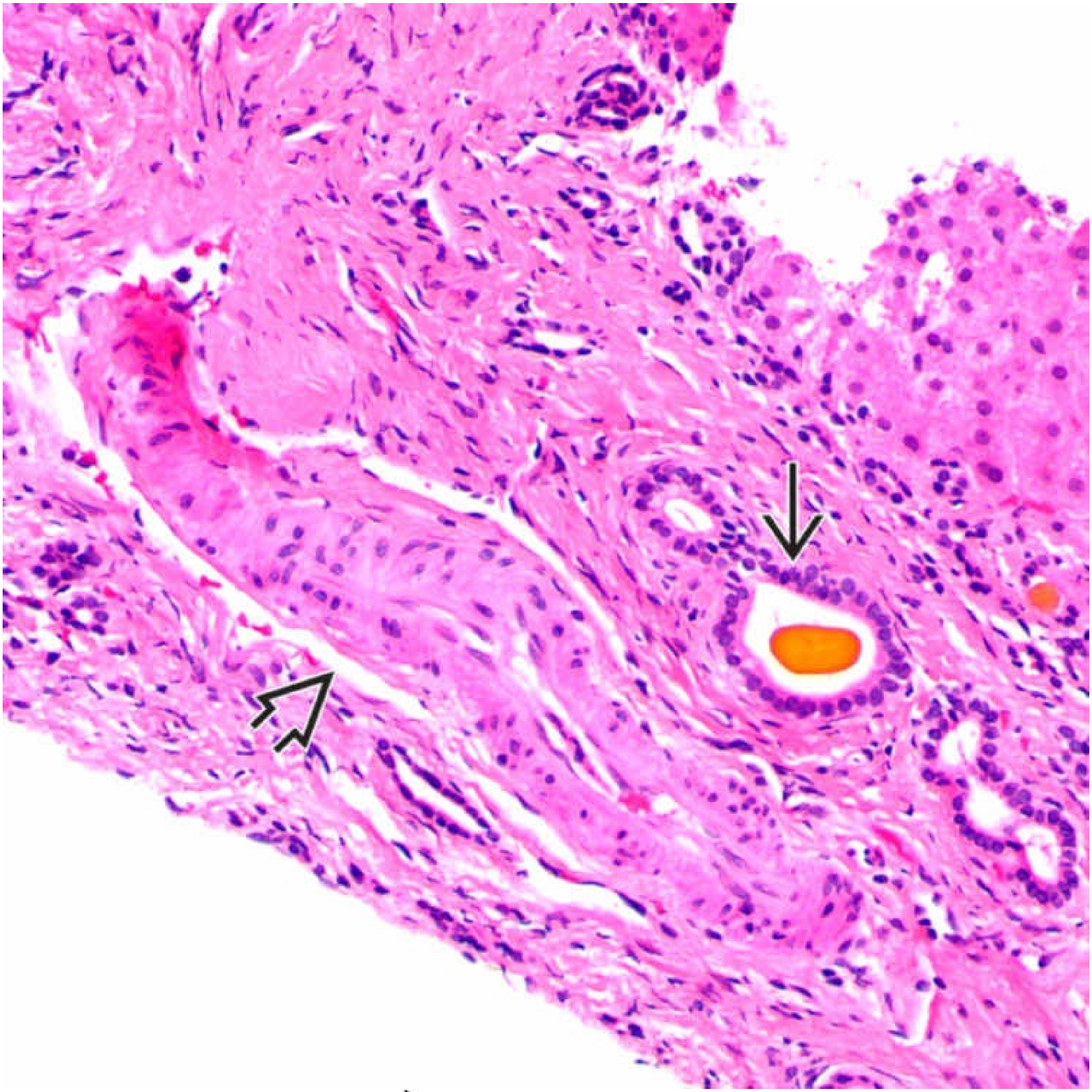
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

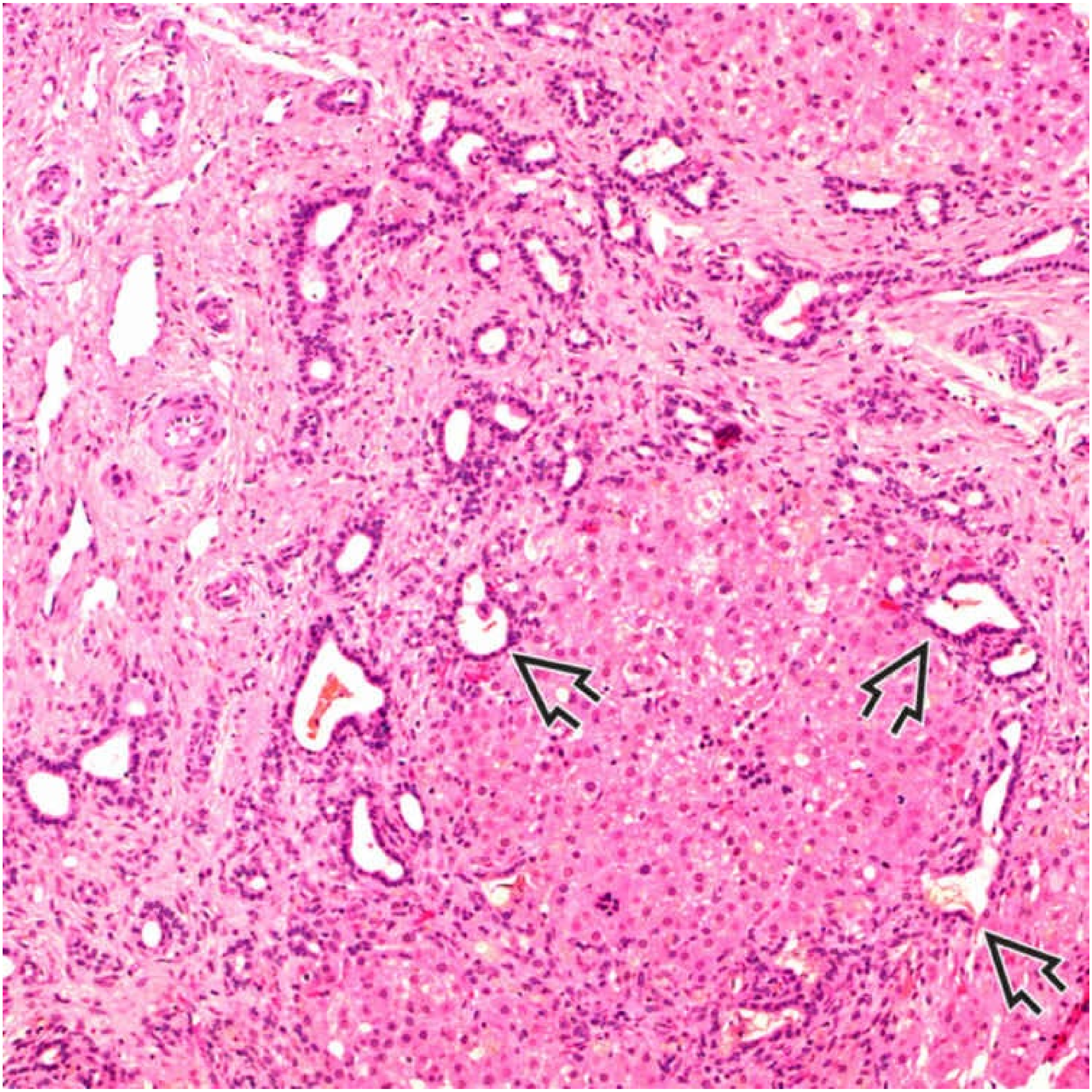
- Teenager or young adult with portal hypertension

Pathologic Interpretation Pearls

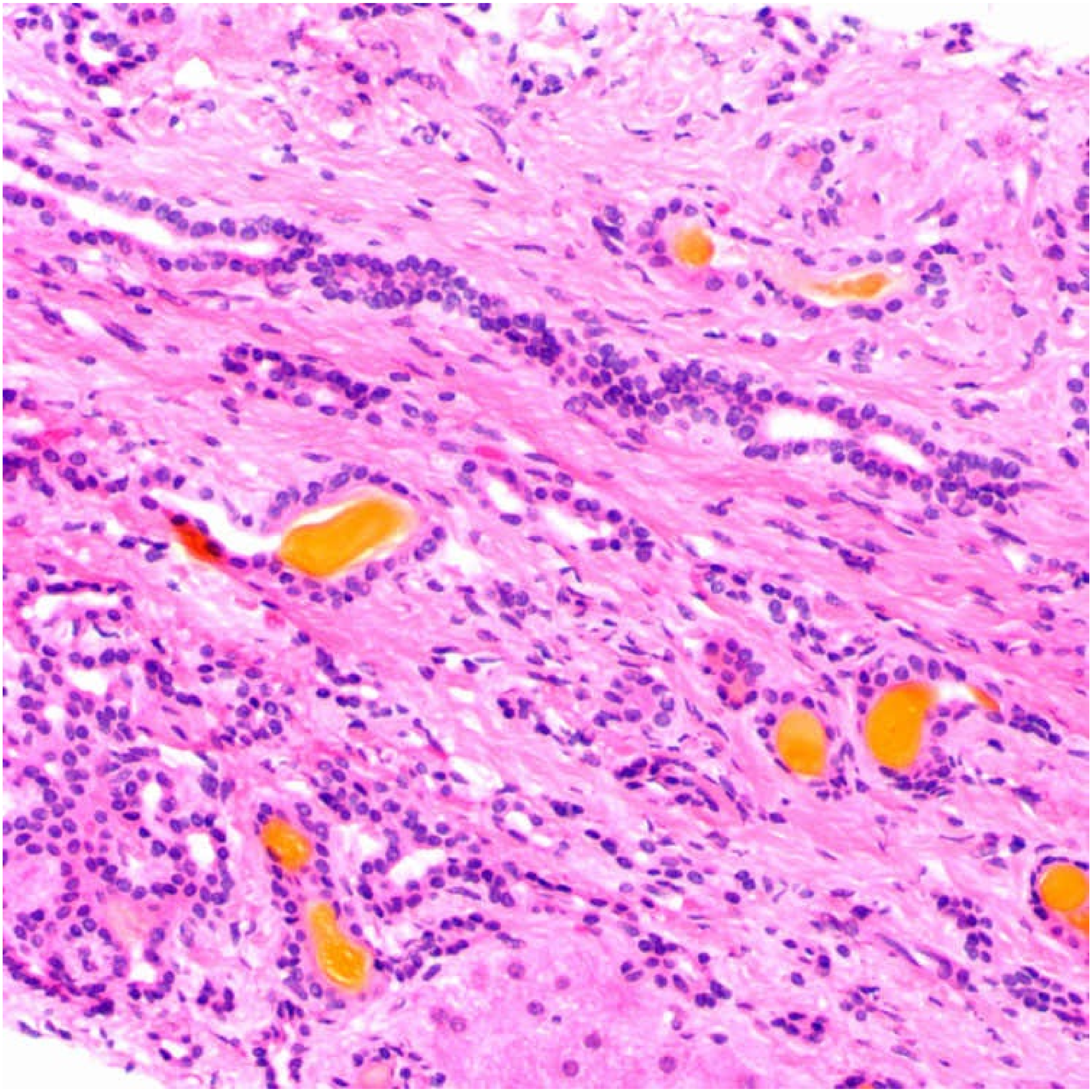
- Characteristic lesion is combination of portal fibrosis and persistence of excess embryonic bile ducts



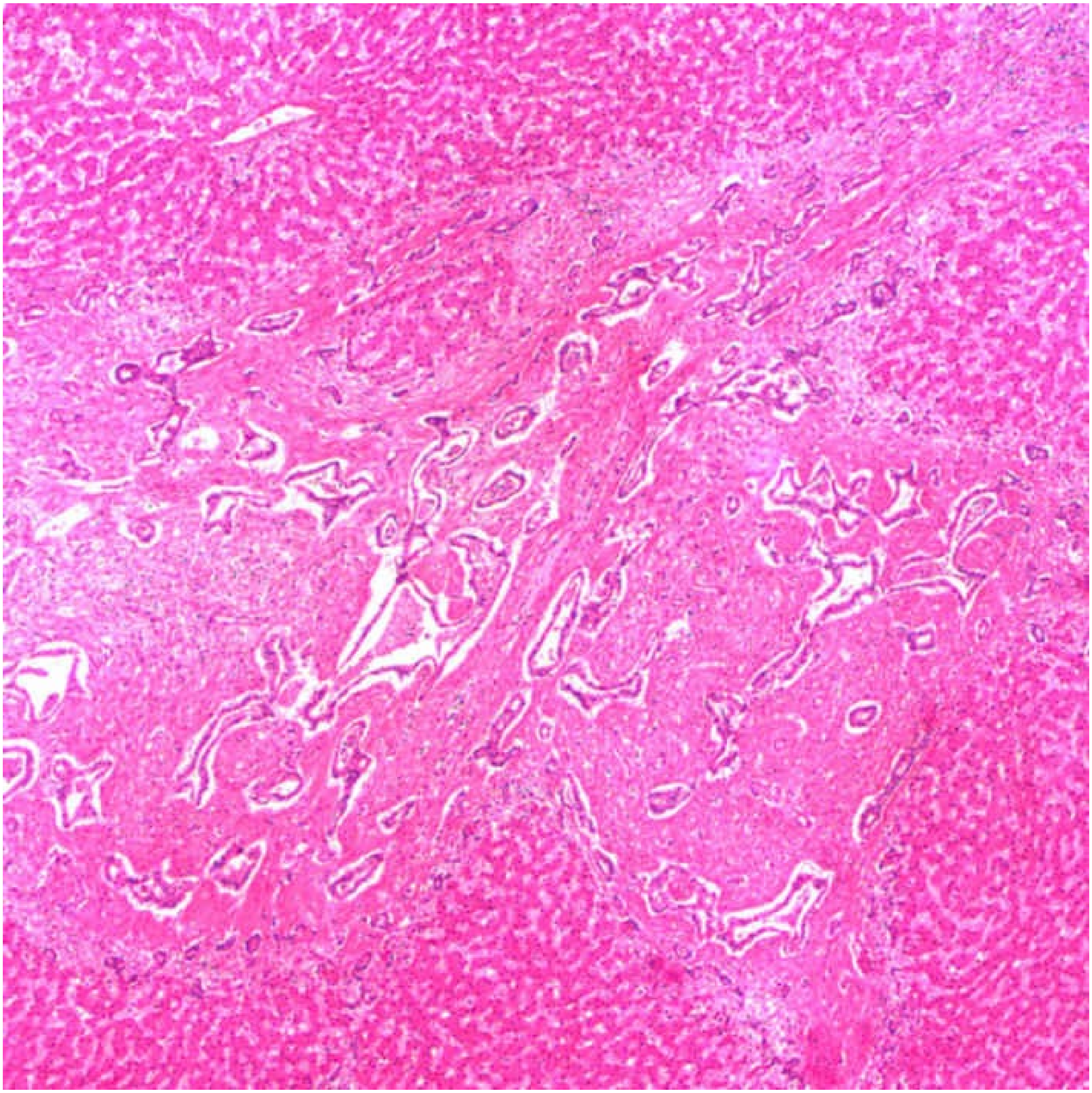
A hypertrophic hepatic artery branch ➩ is seen in a case of congenital hepatic fibrosis. Note inspissated bile in a duct → .



In congenital hepatic fibrosis, some of the ducts are characteristically located at the interface with the liver parenchyma ➭ .



The aberrantly formed bile ducts are lined by cuboidal or low columnar biliary epithelium, and some contain inspissated bile.



Low-power view shows marked portal expansion and numerous irregularly shaped bile ducts. The lobular architecture in adjacent parenchyma is well maintained with normal central veins.

SELECTED REFERENCES

1. Gunay-Aygun, M, et al. Characteristics of congenital hepatic fibrosis in a large cohort of patients with autosomal recessive polycystic kidney disease. *Gastroenterology*. 2013; 144(1):112–121.
2. Srinath, A, et al. Congenital hepatic fibrosis and autosomal recessive polycystic kidney disease. *J Pediatr Gastroenterol Nutr*. 2012; 54(5):580–587.

Polycystic Liver Disease

KEY FACTS

Etiology/Pathogenesis

- Frequent association with autosomal dominant polycystic kidney disease (ADPKD) but also occurring in isolated form
- Autosomal dominant inheritance
- Developing from ductal plate malformation

Clinical Issues

- ADPKD affecting 1 in 500-1,000 individuals
  - PLD occurring in 30-90% of patients
  - Age-dependent increase in number and size of liver cysts
  - Higher prevalence of PLD in women
- Isolated PLD affecting < 0.01% of population
- Asymptomatic in ~ 80% of patients
- Symptomatology due to hepatomegaly with compression of adjacent structures
  - Treatment options include aspiration of large dominant cyst, sclerotherapy, cyst fenestration, somatostatin analogues, partial hepatectomy, and liver transplantation
- Renal failure is main complication of ADPKD

Macroscopic

- Hepatomegaly weighing up to 13 kg
- Cysts varying from < 1 mm to > 12 cm in diameter
- Occasionally 1 lobe involved (usually left lobe)
- Clear, colorless, or straw-colored cyst fluid

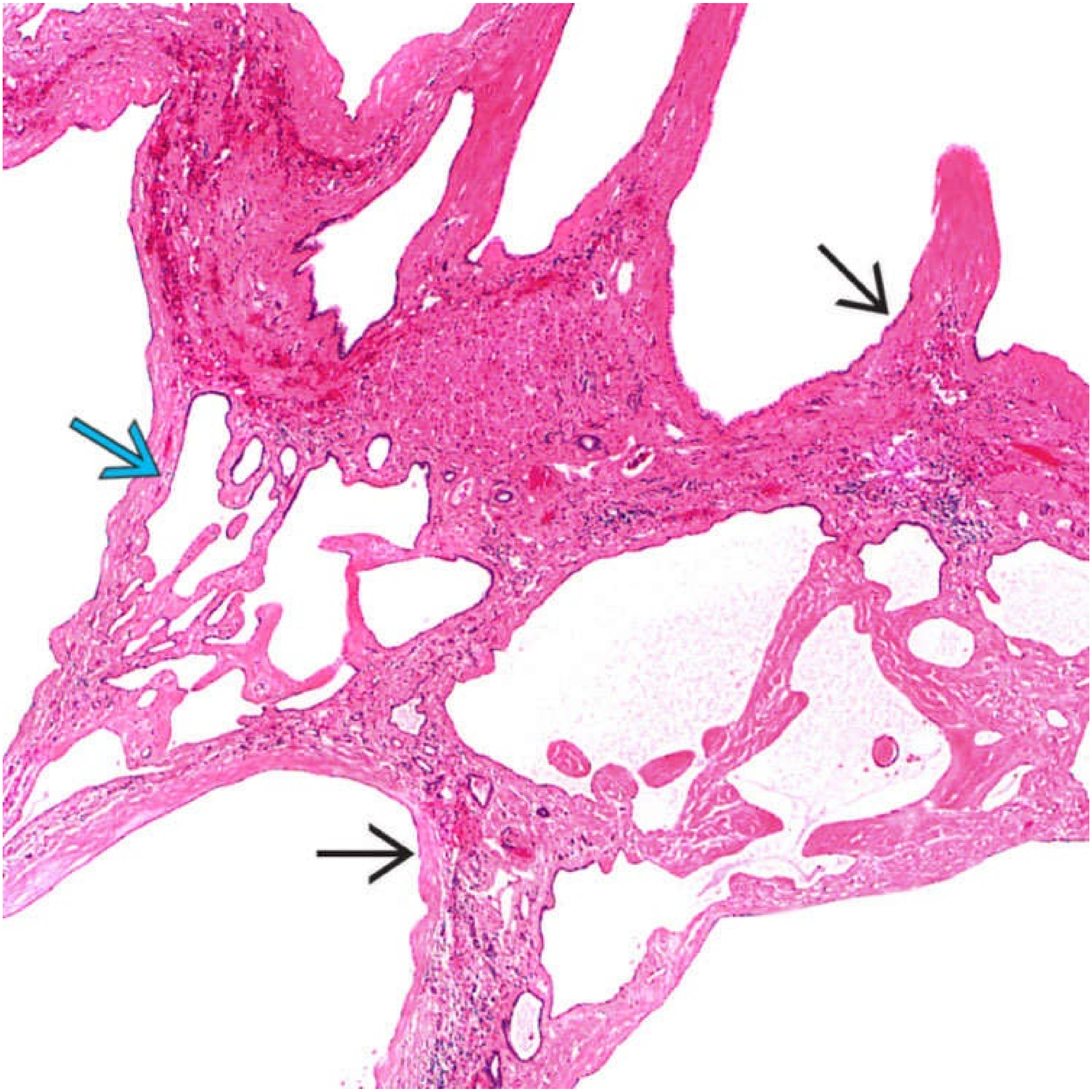
Molecular

- Mutations in *PKD1* gene seen in 80-85% of ADPKD cases
- Mutations in *PKD2* gene seen in 15-20% of ADPKD cases
- Mutations in *PRKCSH*, *SEC63*, and *LRP5* genes in isolated PLD cases

Microscopic

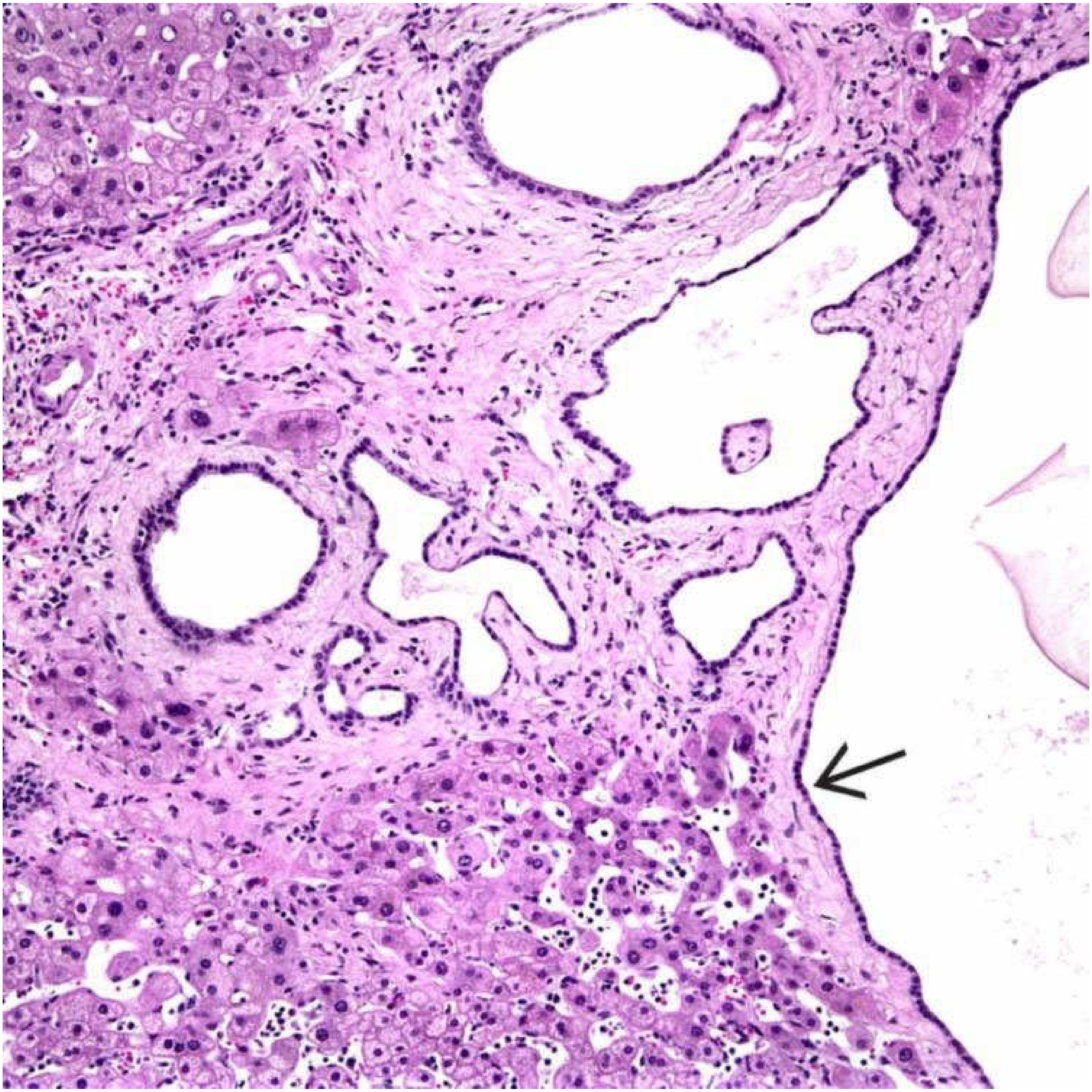
- Numerous variably sized cysts lined by single layer of cuboidal or flattened biliary epithelium
- Lack of communication with biliary tree
- von Meyenburg complexes commonly present
- Fibrosis and hyalinization in collapsed cysts, which may resemble corpora atretica or fibrosa of ovary

Gross Appearance
This case of polycystic liver disease features massive involvement by numerous variably sized cysts, which are present throughout the liver. Note that the cyst walls are thin and smooth ⇒ .

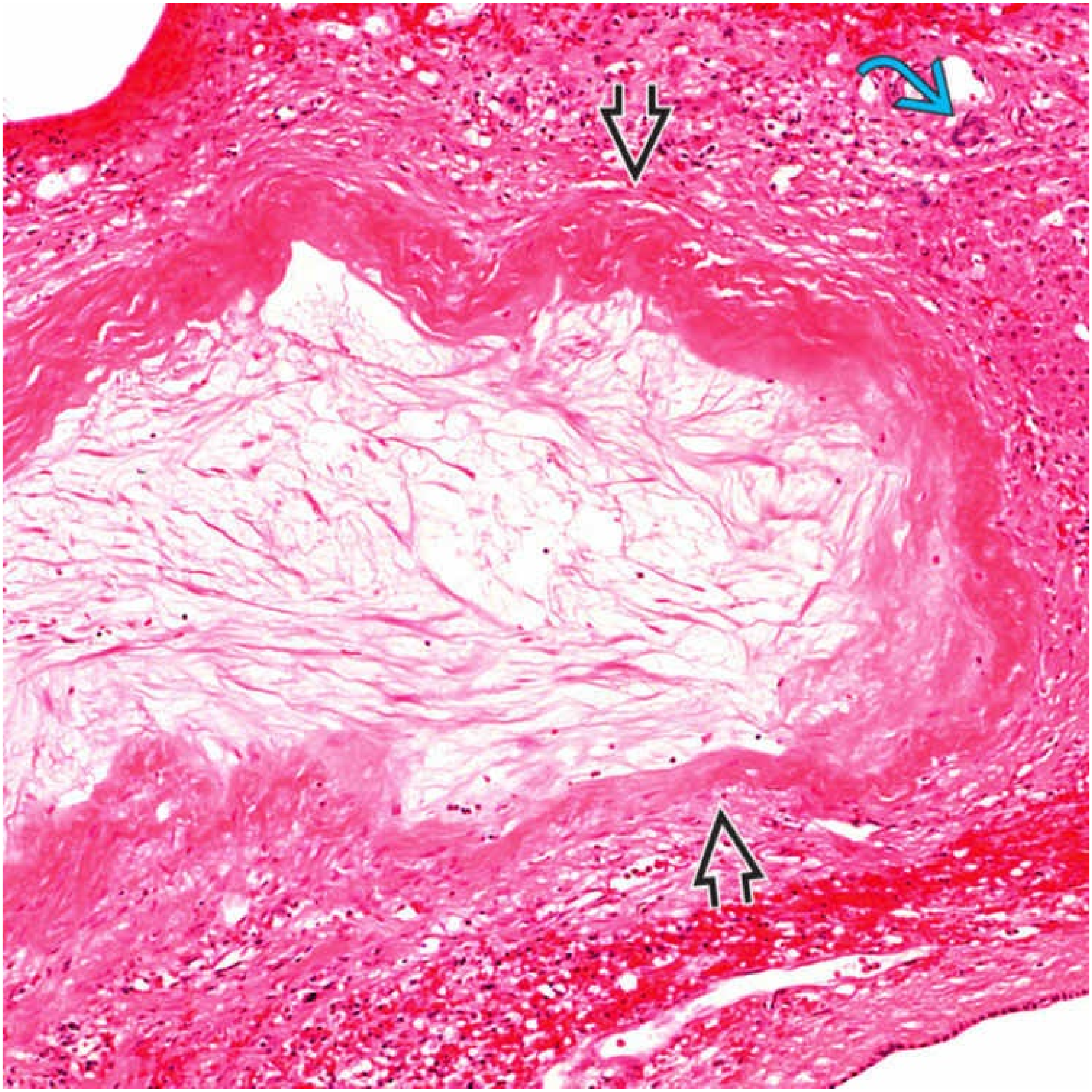


Multiple Cystic Spaces

Low-power view shows numerous cystic spaces lined by a single layer of epithelial cells →, supported by variable amounts of connective tissue. Only minimal liver parenchyma remains. A von Meyenburg complex → is present. Slightly proteinaceous fluid is present in some of the cystic spaces.



von Meyenburg Complex
A von Meyenburg complex is present adjacent to a cyst →. The von Meyenburg complex is composed of dilated, angulated biliary structures. These are commonly seen in polycystic liver disease.



Collapsed Cyst

A collapsed cyst consists of a corrugated and hyalinized wall. The lumen is filled with loose connective tissue, resembling a corpus atreticum or fibrosum of the ovary. Note the presence of residual liver parenchyma with a normal bile duct.

TERMINOLOGY

Abbreviations

- Polycystic liver disease (PLD)
- Autosomal dominant polycystic kidney disease (ADPKD)

Definitions

- Genetic disorder characterized by progressive development of multiple liver cysts

ETIOLOGY/PATHOGENESIS

Hereditary Anomaly

- Associated with ADPKD
  - Mutations in *PKD1* gene encoding polycystin-1 seen in 80-85% of cases
  - Mutations in *PKD2* gene encoding polycystin-2 seen in 15-20% of cases
- Isolated PLD
  - Mutations in *PRKCSH* gene encoding hepatocystin
  - Mutations in *SEC63* gene encoding Sec63p protein
  - Mutation in *LRP5* gene encoding a transmembrane protein
  - Also autosomal dominant inheritance
- Developing from embryonic ductal plate malformation (von Meyenburg complexes)
- Evolving through overgrowth and dilatation into cysts
- Loss of continuity with biliary tree

CLINICAL ISSUES

Epidemiology

- Incidence
  - ADPKD affecting 1 in 500-1,000 individuals
  - PLD occurring in 30-90% of patients with ADPKD
- Isolated PLD affecting < 0.01% of population
- Age
  - Age-dependent increase in number and size of cysts in liver in patients with ADPKD
    - 20% in 3rd decade of life
    - 75% by 7th decade
- Sex
  - Higher prevalence of PLD in women with ADPKD
    - 58-75% in women vs. 42-62% in men
  - More numerous and larger liver cysts in women, presumably due to stimulatory effects of estrogen
    - History of multiple pregnancies
    - Prolonged exposure to oral contraceptives or hormone replacement therapy

Presentation

- Asymptomatic in ~ 80% of patients
  - Hepatomegaly with compression of adjacent structures
  - Abdominal pain
  - Early satiety
  - Nausea and vomiting
  - Supine dyspnea

    - Lower body edema and ascites
- Other associated medical conditions
    - Asymptomatic cysts in other organs including pancreas, spleen, ovaries, seminal vesicles, and lungs
    - Intracranial aneurysm
    - Valvular heart disease such as mitral valve prolapse

Laboratory Tests

- Usually normal liver tests

Treatment

- Percutaneous aspiration of large dominant cyst
- Sclerotherapy
- Cyst fenestration
- Somatostatin analogues
- Partial hepatectomy
- Liver transplantation

Prognosis

- Rupture of cyst
- Intracystic hemorrhage
- Cyst infection
- Rarely portal hypertension or hepatic failure
- Renal failure is main complication of ADPKD

IMAGING

Gigot Radiographic Classification

- Type 1: Limited number (< 10) of large cysts with large areas of noncystic liver parenchyma
- Type 2: Diffuse involvement by medium-sized cysts with large areas of noncystic liver parenchyma
- Type 3: Massive involvement by small- and medium-sized cysts with only a few areas of noncystic liver parenchyma

MACROSCOPIC

General Features

- Hepatomegaly weighing up to 13 kg
    - Cysts varying from < 1 mm to > 12 cm in diameter
    - No communication with biliary tree
- Occasionally 1 lobe involved (usually left lobe)
- Clear, colorless, or straw-colored cyst fluid

MICROSCOPIC

Histologic Features

- Variably sized cysts lined by single layer of cuboidal or flattened biliary epithelium
- Varying amounts of supporting connective tissue
- von Meyenburg complexes commonly present
- Neutrophil infiltration in infected cysts
- Fibrosis and hyalinization in collapsed cysts, which may resemble corpora atretica or fibrosa of ovary
- Dystrophic calcification may be seen in cyst wall

DIFFERENTIAL DIAGNOSIS

Simple Biliary (Unilocular) Cyst

- Fewer in number with abundant liver parenchyma
- Nonhereditary

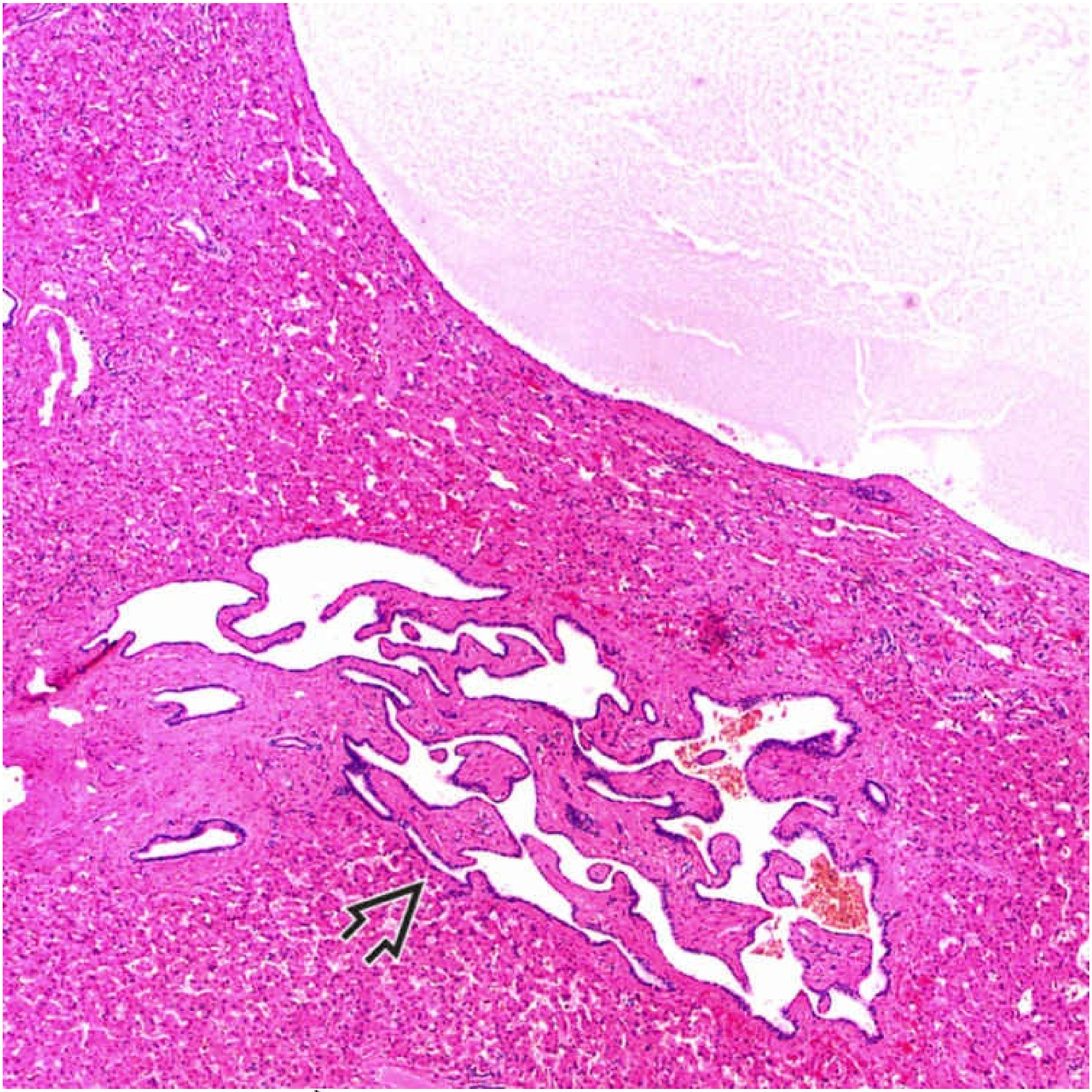
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

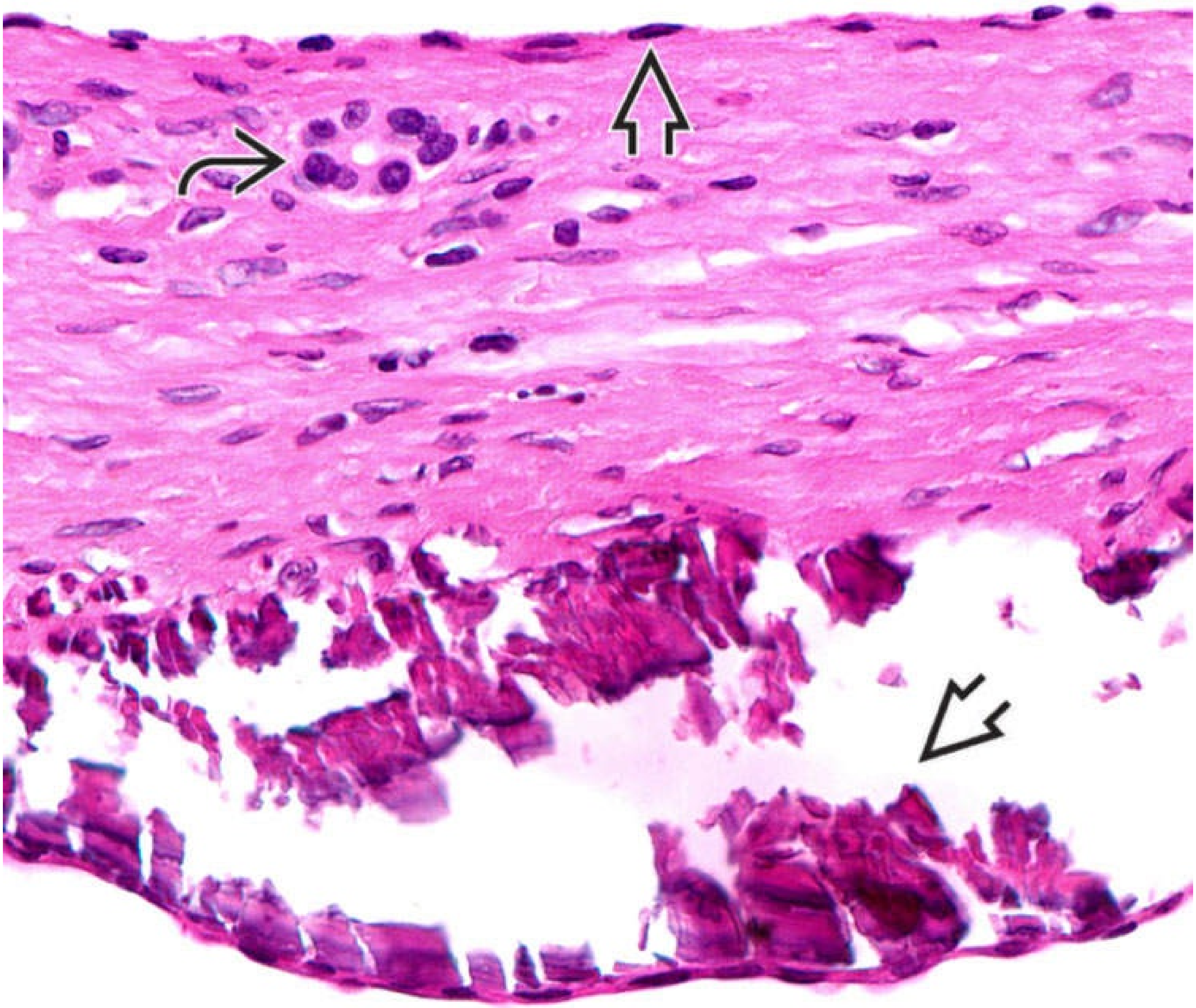
- Usually occurring in setting of ADPKD

Pathologic Interpretation Pearls

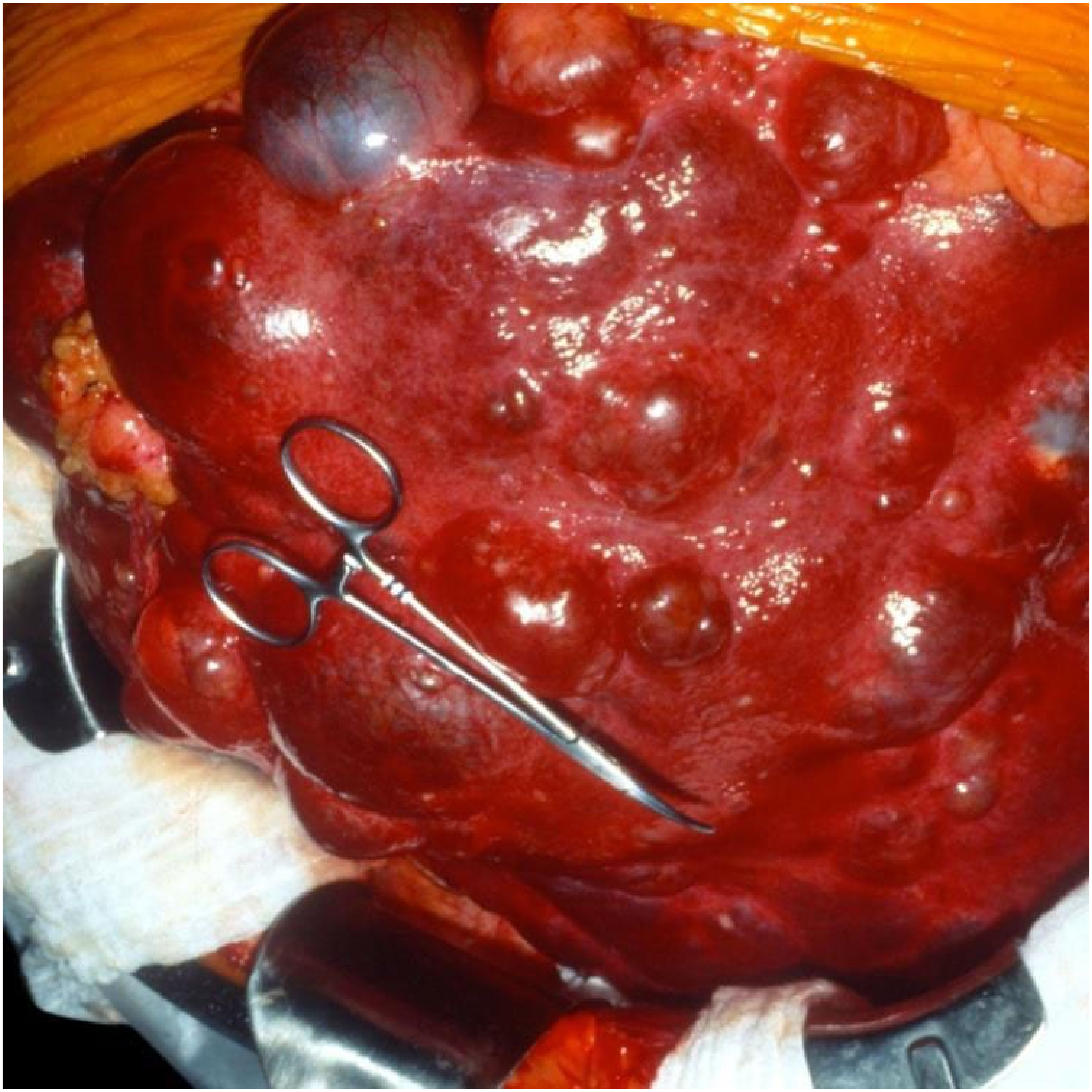
- Diffuse liver involvement by numerous cysts lined by single layer of biliary epithelium



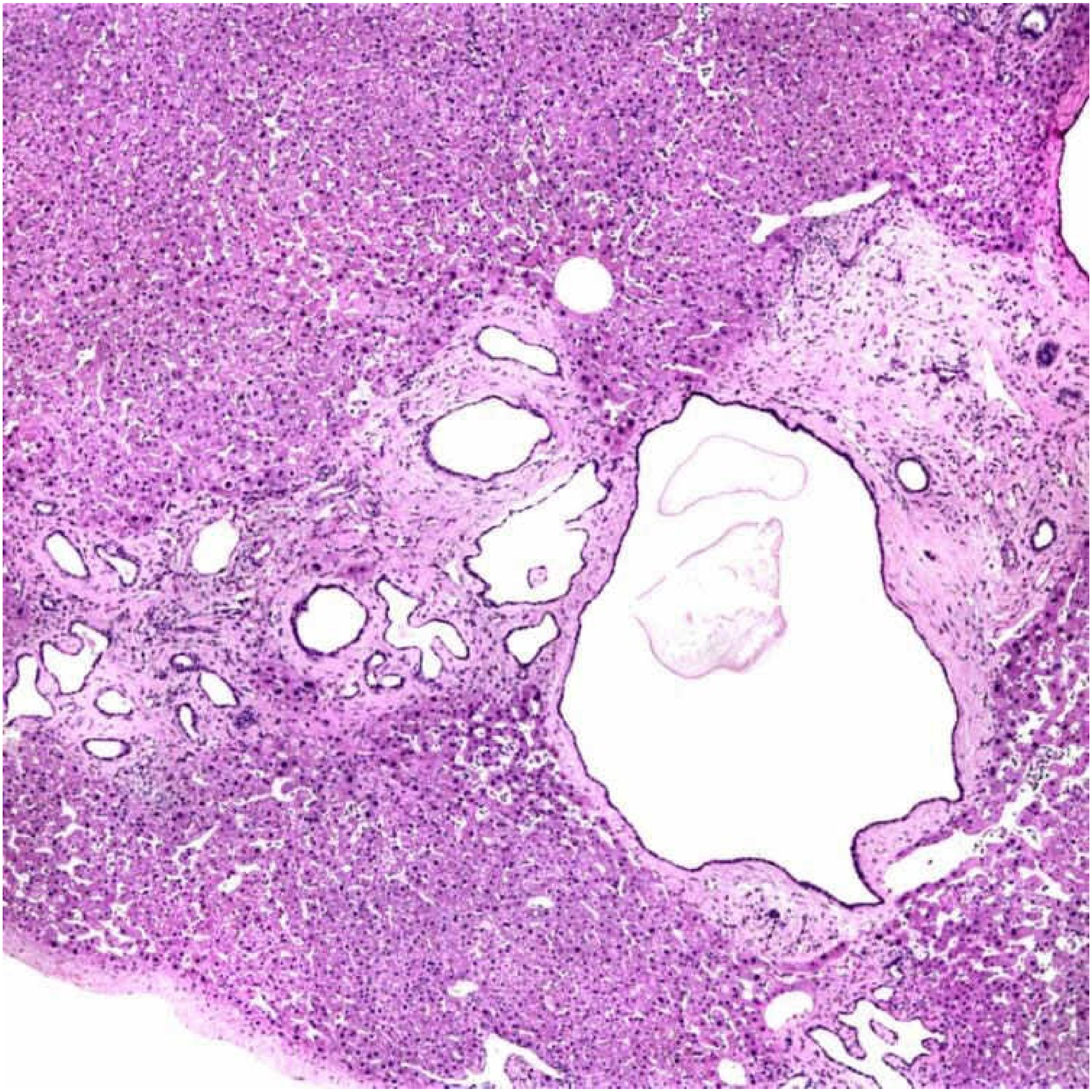
A von Meyenburg complex ➪ is present adjacent to a cyst that contains slightly proteinaceous fluid. von Meyenburg complexes are a characteristic feature of polycystic liver disease.



The biliary epithelium lining the cysts is flattened in this case of polycystic liver disease. Note the presence of fibrosis, dystrophic calcification, and a residual normal bile duct in the cyst wall.



This intraoperative photograph illustrates the surface of the liver and the multiple, variably sized cysts in a patient with polycystic liver disease. (Courtesy G.F. Gray Jr., MD.)



A von Meyenburg complex is present, with an adjacent small cyst lined by a single layer of biliary epithelium.

SELECTED REFERENCES

1. Khan, S, et al. Medical therapy for polycystic liver disease. *Ann R Coll Surg Engl*. 2016; 98(1):18–23.
2. Cnossen, WR, et al. Polycystic liver disease: an overview of pathogenesis, clinical manifestations and management. *Orphanet J Rare Dis*. 2014; 9:69.
3. Perugorria, MJ, et al. Polycystic liver diseases: advanced insights into the molecular mechanisms. *Nat Rev Gastroenterol Hepatol*. 2014; 11(12):750–761.

Caroli Disease

KEY FACTS

Terminology

- Caroli disease: Segmental dilatation of larger intrahepatic bile ducts without other hepatic abnormalities
- Caroli syndrome: Segmental dilatation of larger intrahepatic bile ducts with congenital hepatic fibrosis

Etiology/Pathogenesis

- Total or partial arrest of remodeling of ductal plates during embryogenesis
- Primarily autosomal recessive inheritance but can be autosomal dominant

Clinical Issues

- Characterized by recurrent cholangitis, abscess formation, hepatolithiasis, and biliary cirrhosis
- Cholangiocarcinoma develops in 7% of patients
- Association with polycystic kidney disease

Imaging

- Intrahepatic saccular cysts
- May show characteristic central dot sign or intracystic fibrovascular bridges
- Continuity of cysts to biliary system

Macroscopic

- Segmental saccular dilatations of larger intrahepatic ducts
  - May fill with bile sludge, stones, &/or pus
  - May affect entire liver or limited to 1 lobe, more commonly left

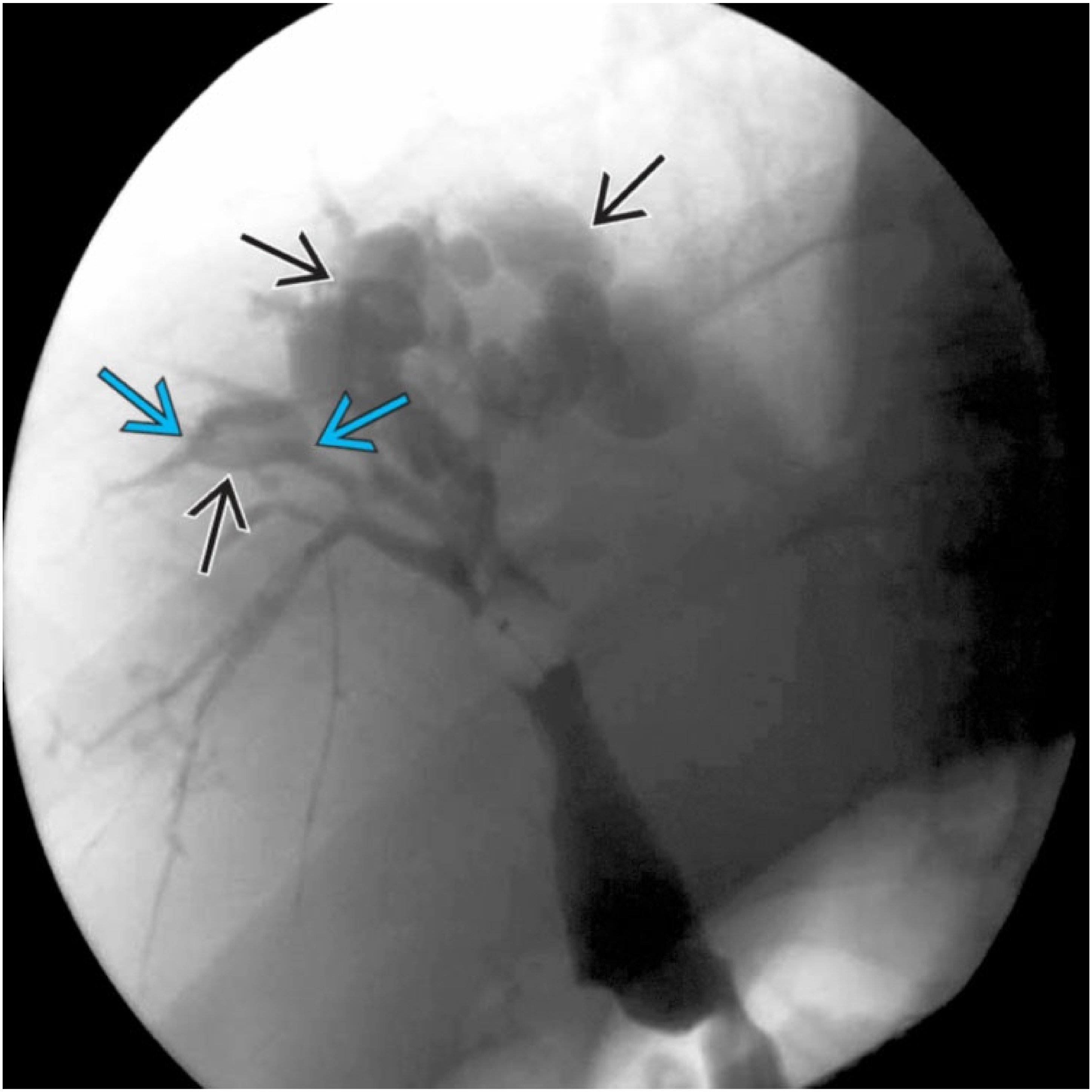
Microscopic

- Dilated ducts may show periductal fibrosis, acute and chronic inflammation, ulceration, or abscess

formation
- Background liver may show features of congenital hepatic fibrosis or biliary cirrhosis

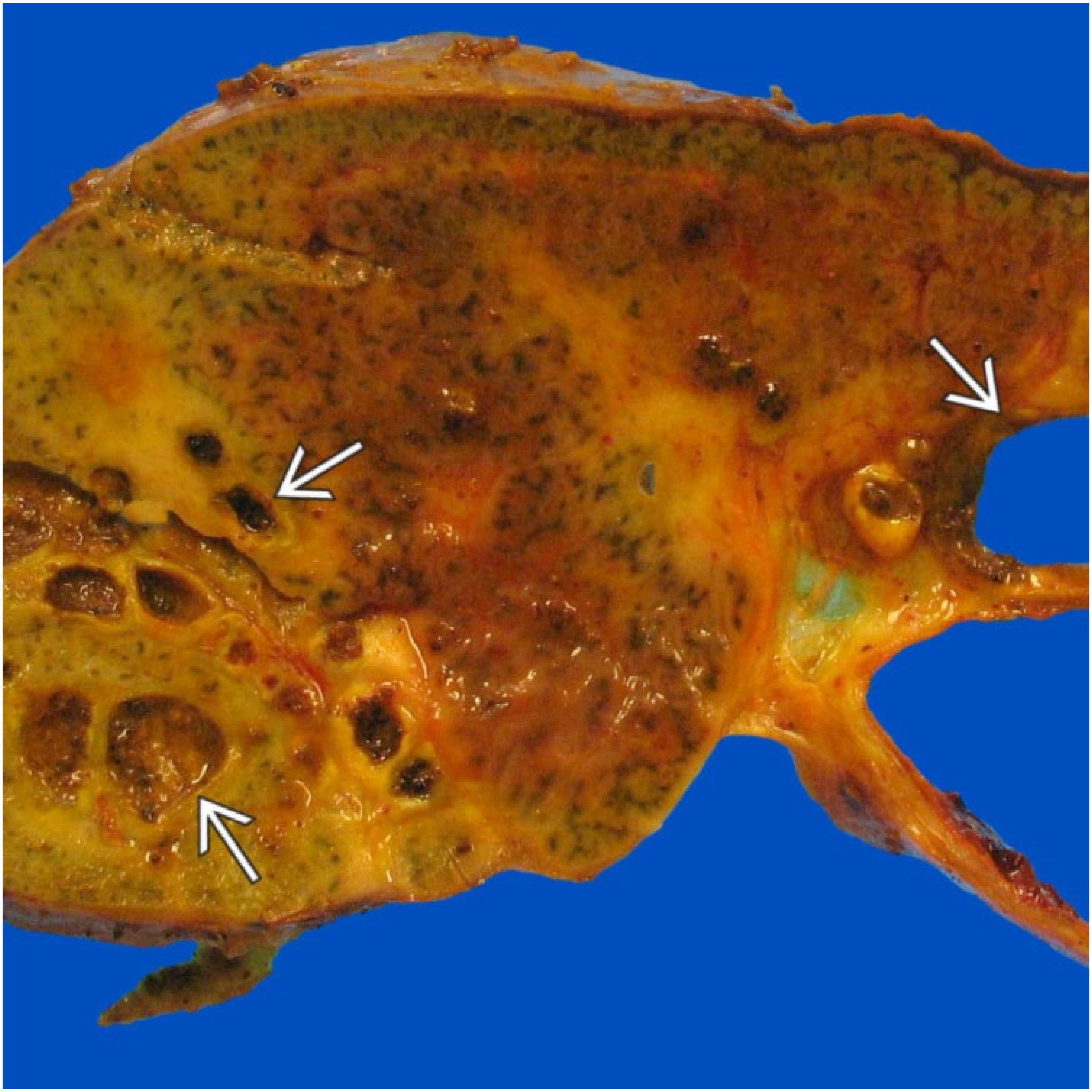
Top Differential Diagnoses

- Primary sclerosing cholangitis
- Recurrent pyogenic cholangitis
- Polycystic liver disease



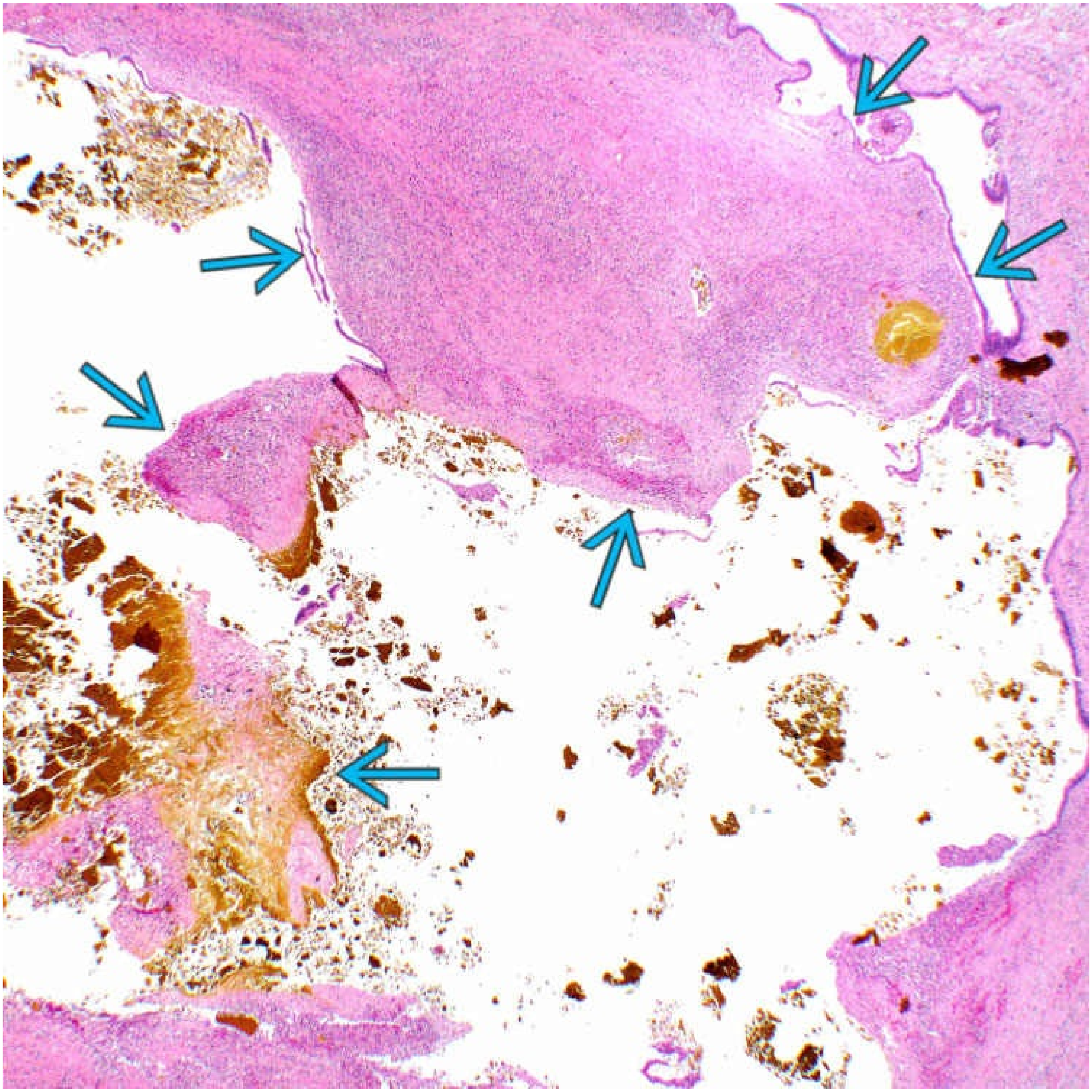
ERCP

Radiologic image obtained by endoscopic retrograde cholangiopancreatography (ERCP) shows saccular dilatations of the intrahepatic bile ducts near the hilum →. Note the connection with normal-appearing ducts → .



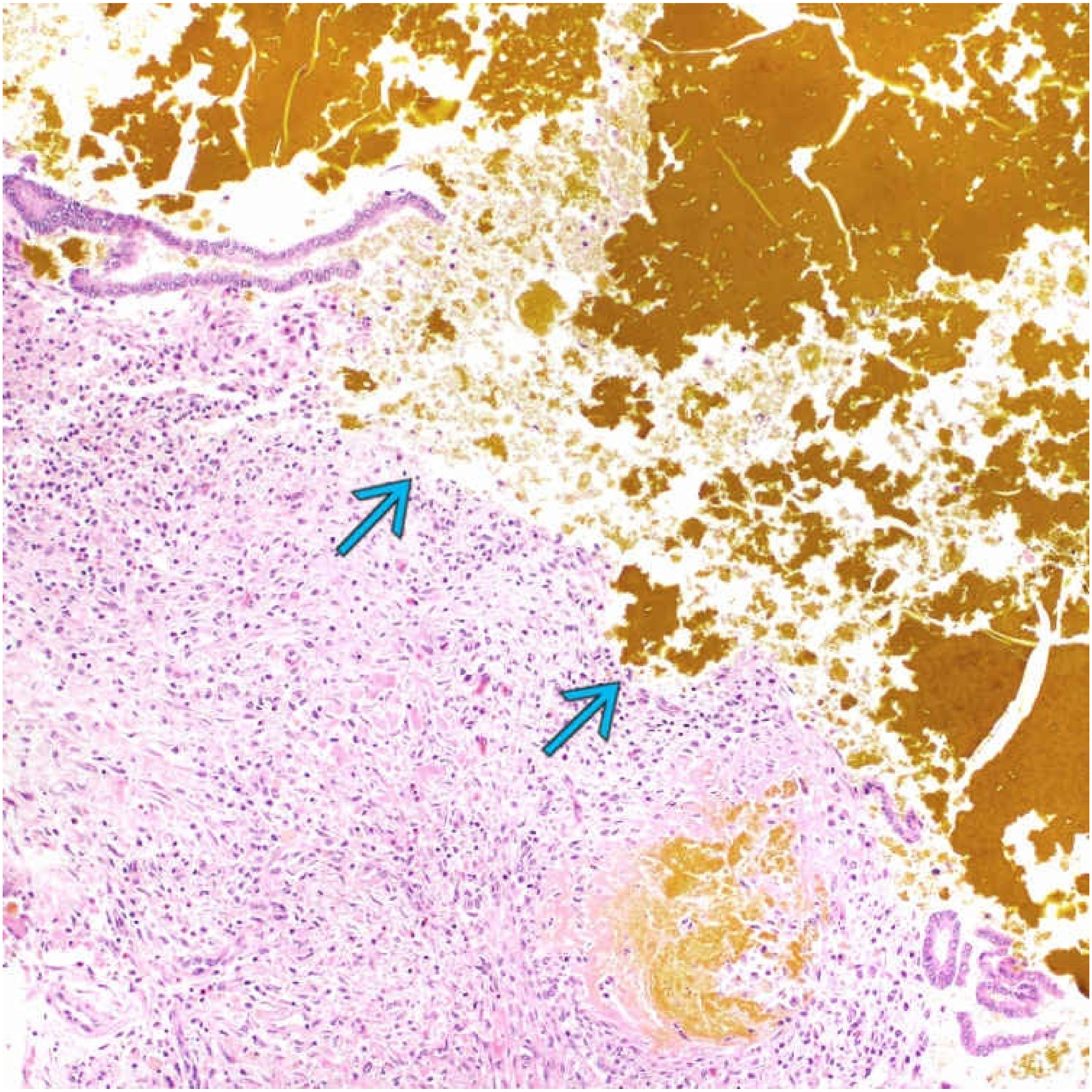
Gross Appearance

This explanted liver shows cystically dilated bile ducts involving both left and right lobes ⇒. Bile sludge is present in the dilated ducts. The background liver shows fibrosis and cholestasis consistent with biliary cirrhosis on the background of congenital hepatic fibrosis.



Dilated Duct Transluminal Bridge

This low-power view shows a massively dilated bile duct with inspissated bile in the lumen. The lining epithelium is partially denuded. A polypoid fibrovascular cord protrudes into the lumen to form a bridge → .



Bile Duct Inflammation
This dilated bile duct shows a mixed inflammatory cell infiltrate in the wall, consisting mainly of histiocytes and neutrophils. Fibrosis is also evident. The luminal surface is eroded by inspissated bile → .

TERMINOLOGY

Synonyms

- Congenital cystic dilatation of intrahepatic biliary tree
- Communicating cavernous ectasia
- Type V choledochal cyst

Definitions

- Caroli disease: Segmental dilatation of larger intrahepatic bile ducts without other hepatic abnormalities
- Caroli syndrome: Segmental dilatation of larger intrahepatic bile ducts in association with congenital hepatic fibrosis

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Total or partial arrest of remodeling of ductal plates during embryogenesis
  - Caroli disease
    - Affects larger ducts, mainly segmental ducts
  - Caroli syndrome
    - Affects larger and smaller ducts, including interlobular ducts
  - Primarily autosomal recessive inheritance, but can be autosomal dominant

Disease Associations

- Autosomal recessive polycystic kidney disease
- Autosomal dominant polycystic kidney disease
- Medullary sponge kidney
- Choledochal cyst

CLINICAL ISSUES

Epidemiology

- Incidence
  - 1 in 1 million persons
  - Caroli syndrome is more frequently reported in literature
- Age
  - 0-82 years, but often diagnosed between 5-20 years

Presentation

- Fever, abdominal pain, jaundice, hepatomegaly
- Portal hypertension in patients with Caroli syndrome

Complications

- Recurrent cholangitis, abscess formation, sepsis
- Hepatolithiasis, biliary obstruction, biliary cirrhosis
- Complications of portal hypertension in patients with Caroli syndrome
- Cholangiocarcinoma develops in 7% of patients
- Amyloidosis

Treatment

- Medical
  - Antibiotics to treat cholangitis
  - Ursodeoxycholic acid to promote bile flow
- Surgical
  - Internal and external drainage
  - Sphincterotomy, stone extraction, lithotripsy
  - Partial hepatectomy
  - Liver or combined liver/kidney transplantation

Prognosis

- Uncontrolled biliary infection may lead to death within 5-10 years after onset of recurrent cholangitis

IMAGING

General Features

- Intrahepatic saccular cysts by ultrasound, CT, and MR
  - May show characteristic central dot sign or intracystic fibrovascular bridges
- Continuity of cysts to biliary system by cholangiography

MACROSCOPIC

General Features

- Segmental saccular dilatations of larger intrahepatic ducts
  - Usually 1.0-4.5 cm in diameter, separated by segments of normal-appearing ducts
  - May fill with bile sludge, stones, &/or pus
  - May affect entire liver or be limited to 1 lobe, more commonly left lobe

MICROSCOPIC

Histologic Features

- Dilated ducts may show periductal fibrosis, acute and chronic inflammation, ulceration, or abscess formation
  - Lining epithelium may be normal-appearing, inflamed, reactive, hyperplastic, or dysplastic
  - Inspissated bile or calcareous material may be present in lumina
  - Transluminal fibrovascular bridges or polypoid intraluminal protrusions may be present
    - Explains central dot sign by imaging
  - Proliferation of peribiliary glands may be seen
- Background liver shows features of congenital hepatic fibrosis in cases of Caroli syndrome
  - Features of biliary cirrhosis may be seen

DIFFERENTIAL DIAGNOSIS

Primary Sclerosing Cholangitis

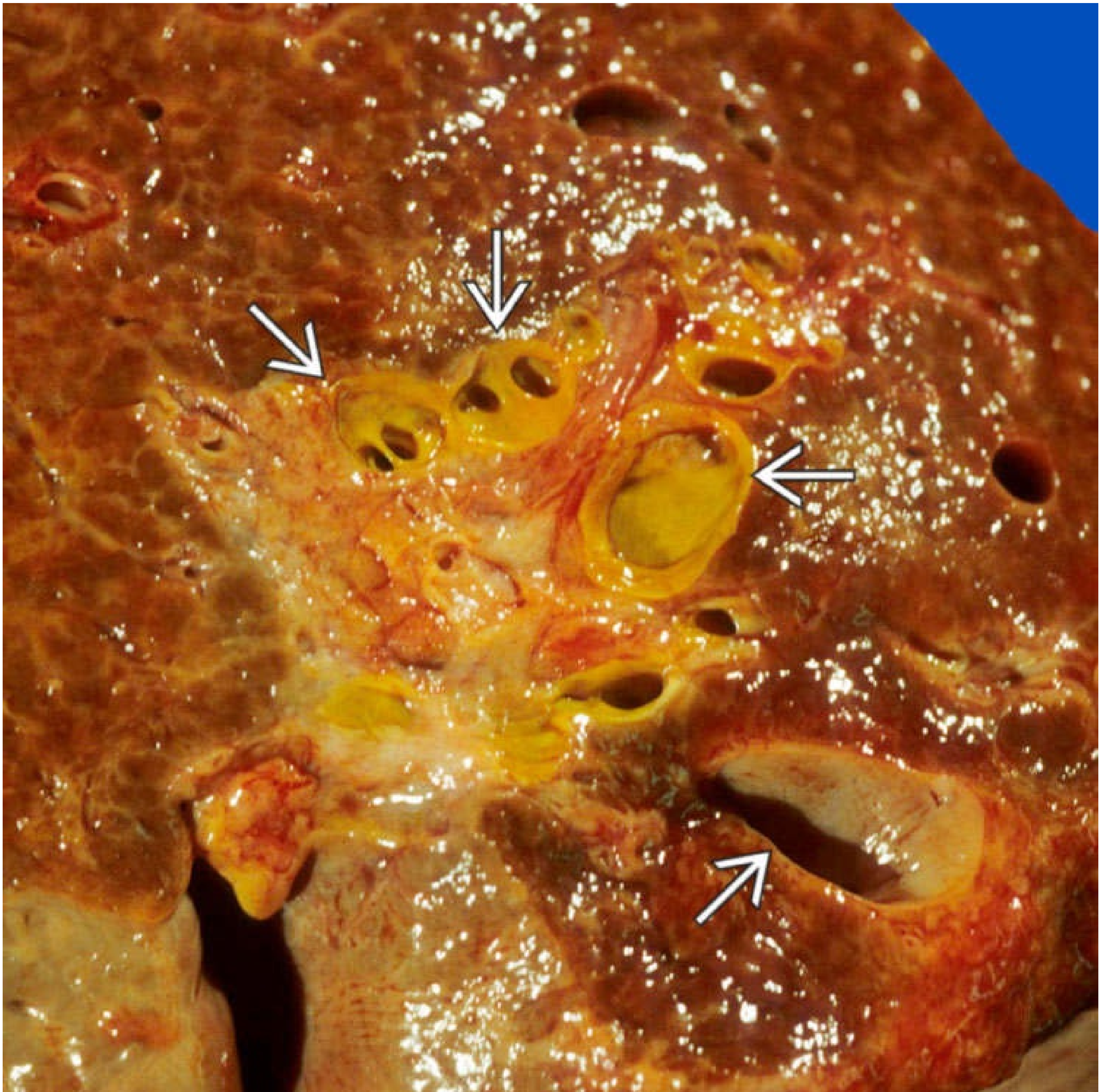
- Characteristic beaded appearance by cholangiography
- Frequent association with inflammatory bowel disease
- Onion skin-type periduct fibrosis

Recurrent Pyogenic Cholangitis

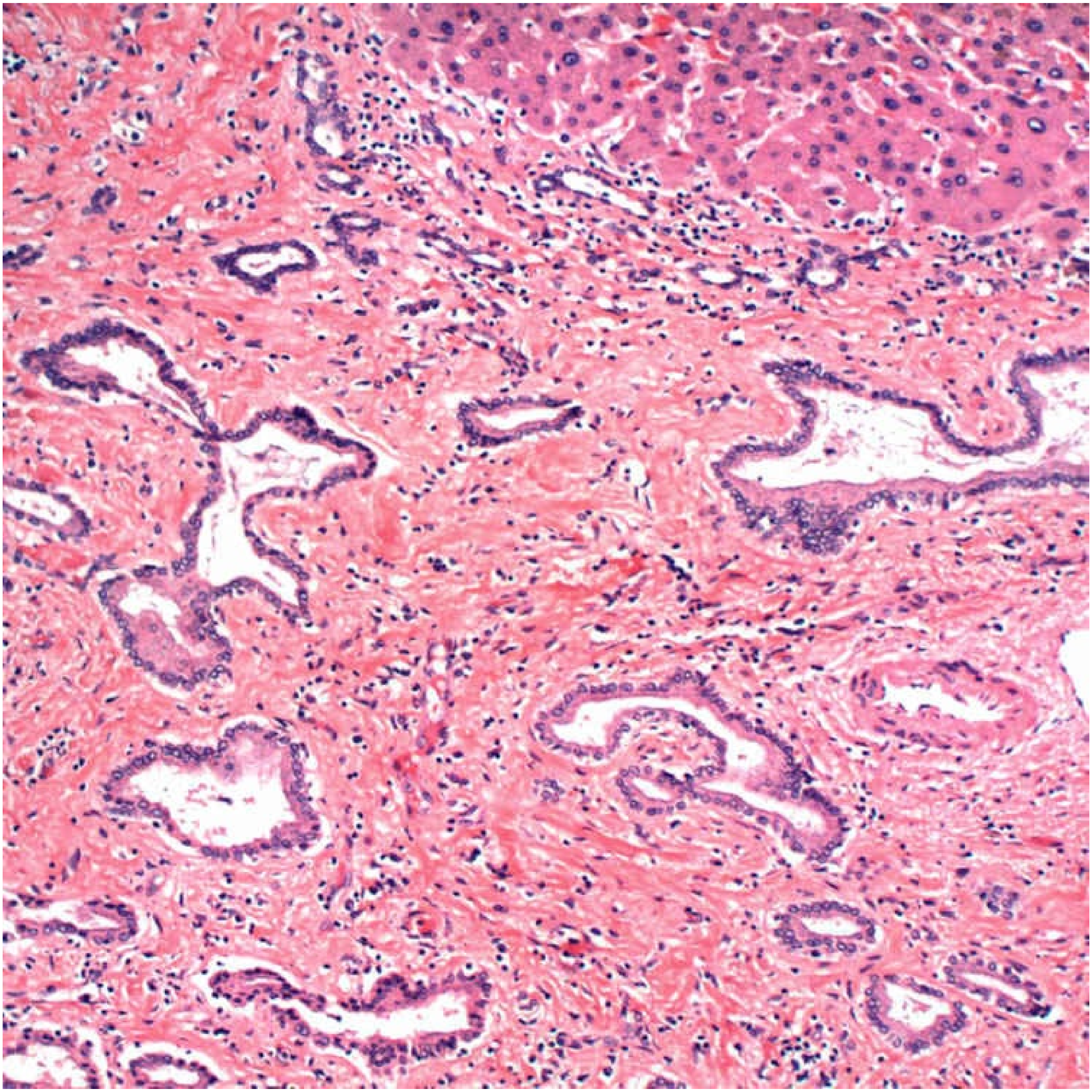
- Primarily seen in Far East or among Asian immigrants
  - a.k.a. oriental cholangiohepatitis
- Average age at presentation: 50s and 60s

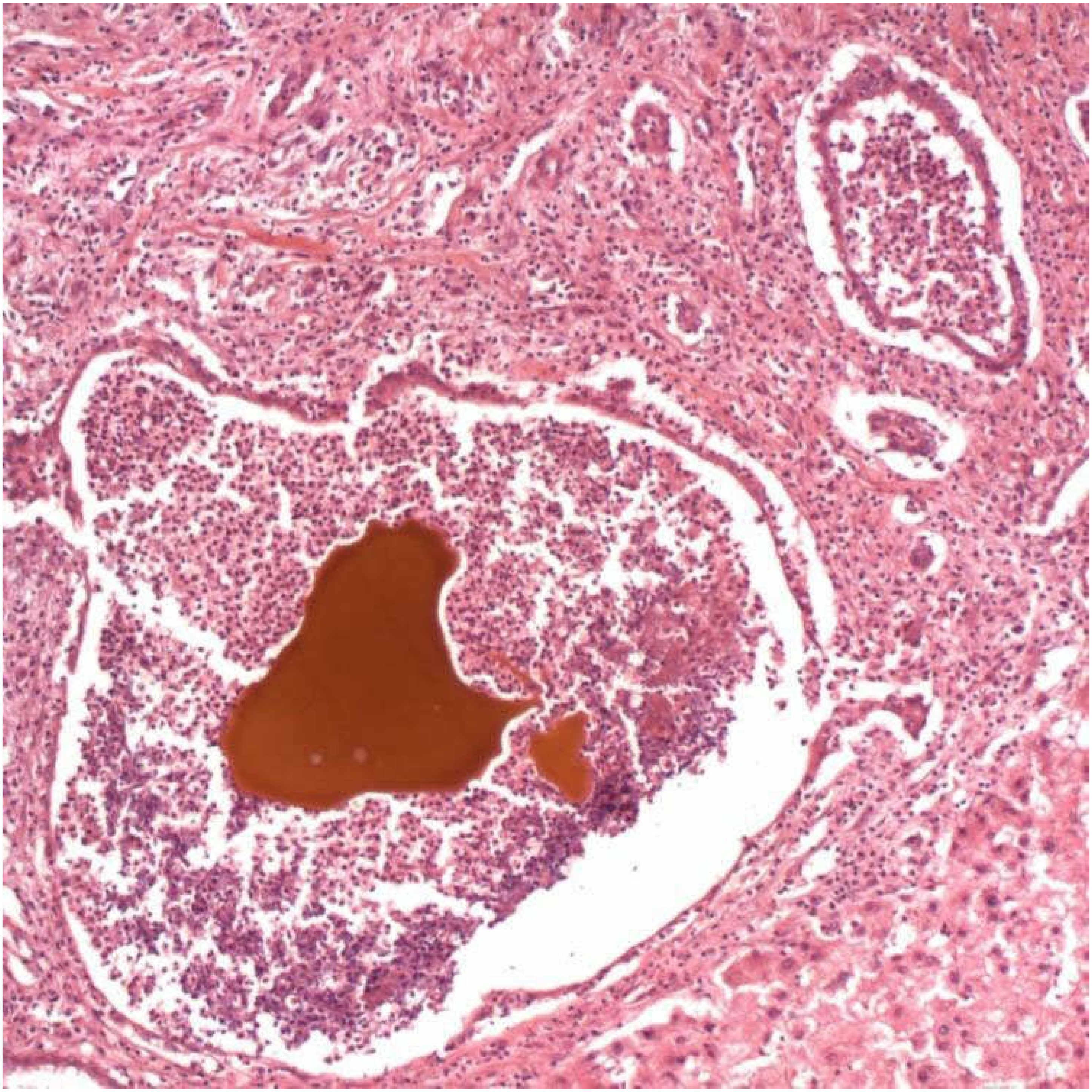
Polycystic Liver Disease

- Cysts only rarely communicate with bile ducts

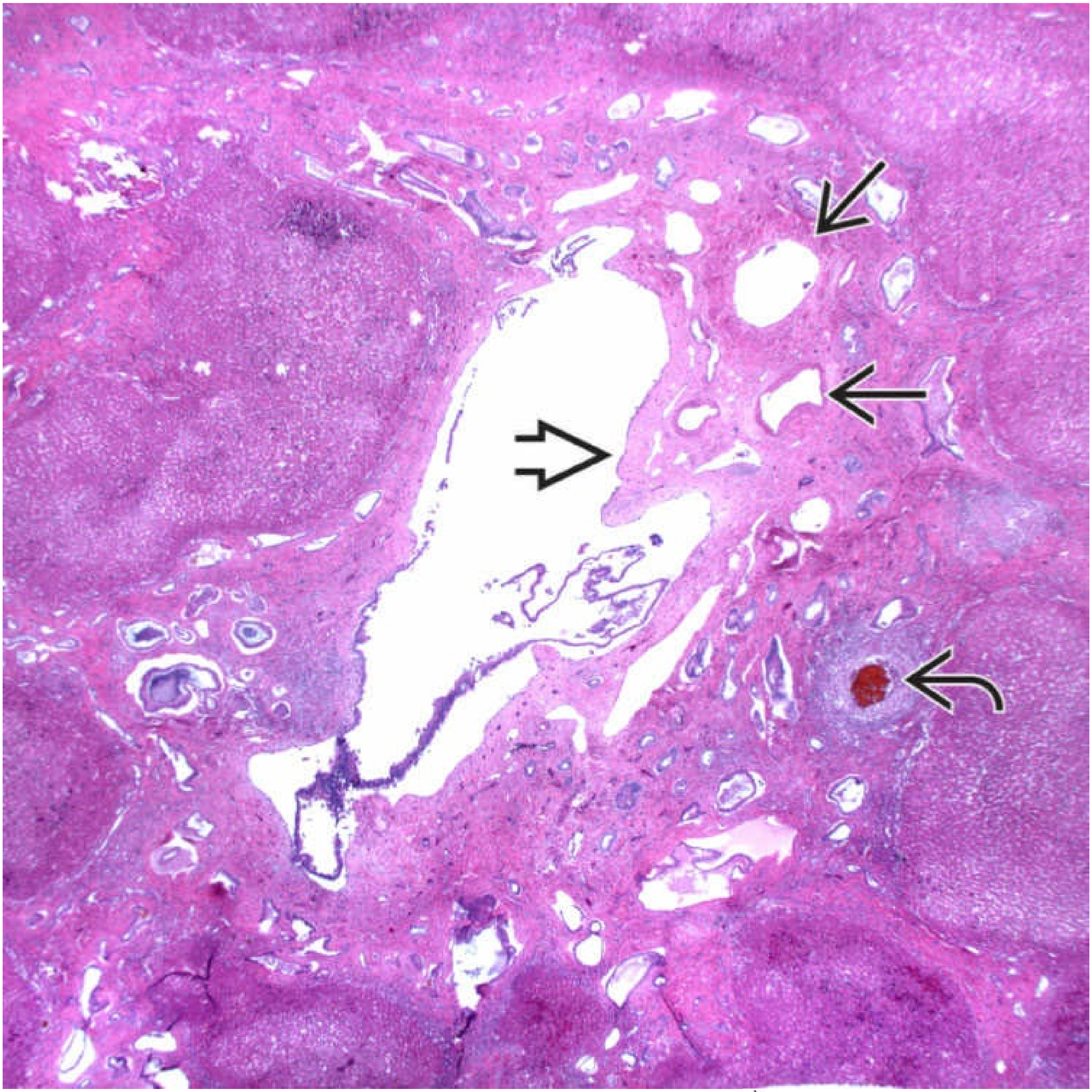


Gross photograph of liver shows clusters of dilated and cystic intrahepatic bile ducts ⇒ .


This section of a liver with Caroli syndrome shows a background of congenital hepatic fibrosis and a proliferation of abnormal ducts with papillary infolding embedded within collagenous stroma.



An explanted liver in Caroli syndrome shows areas with suppurative cholangitis, with numerous neutrophils and inspissated bile within ducts.



A very large bile duct that is out of proportion to its accompanying vessels → is seen at low power. Notice the polypoid protrusion of connective tissue into the duct lumen ⇨. There is a proliferation of small ducts as well, 1 of which is inspissated with bile ↷.

SELECTED REFERENCES

1. Wang, ZX, et al. Clinical classification of Caroli's disease: an analysis of 30 patients. *HPB (Oxford)*. 2015; 17(3):278–283.
2. Zhang, DY, et al. Caroli's disease: a report of 14 patients and review of the literature. *J Dig Dis*. 2012; 13(9):491–495.
3. Tsui, WM, et al. Primary hepatolithiasis, recurrent pyogenic cholangitis, and oriental cholangiohepatitis: a tale of 3 countries. *Adv Anat Pathol*. 2011; 18(4):318–328.
4. Ananthakrishnan, AN, et al. Caroli's disease: identification and treatment strategy. *Curr*

Gastroenterol Rep. 2007; 9(2):151–155.

SECTION 2
INFECTIOUS DISORDERS

OUTLINE

Overview of Hepatitis

TERMINOLOGY

Definitions

- General classification
  - ○ Chronic hepatitis
  - – Persistent, often progressive inflammatory process characterized by lymphocytic inflammation of portal tracts with varying degrees of parenchymal inflammation, hepatocellular injury, and fibrosis
  - □ Chronicity judged in several ways: Clinical, laboratory, morphologic
  - □ Practically defined as 6 months or more of elevated transaminases

○ Acute hepatitis

– Active hepatocellular damage and necrosis

□ Usually of short &/or self-limited duration

□ Most often due to viral infection or adverse drug reaction

□ Infrequently biopsied because diagnosis usually made by clinical or laboratory data

ETIOLOGY/PATHOGENESIS

Viral Hepatitis

- Hepatotropic viruses (A, B, C, E)
- Other viruses, such as Epstein-Barr virus, CMV

Autoimmune Hepatitis

- Type 1: ANA/SMA(+), hypergammaglobulinemia, concurrent autoimmune diseases
- Type 2: Anti-LKM antibodies, more likely to develop cirrhosis
- Type 3: Less well characterized; anti-SLA/LP antibodies; may have AMA(+)

Drug-Associated Hepatitis

- Necroinflammatory
  - ○ Acetaminophen, phenytoin, Macrodantin, sulphonamides
- Cholestatic

- Many antibiotics, steroids
- Granulomatous
  - Allopurinol, many antibiotics, phenytoin

Other

- Wilson disease
  - α-1-antitrypsin deficiency
  - Nonspecific reactive hepatitis
  - Reaction to extrahepatic infection or neoplasm, severe systemic illness, or to adjacent mass lesion in liver

CLINICAL IMPLICATIONS

Clinical Presentation

- Fatigue
- Malaise
- Jaundice
- Anorexia
- Fever
- Nausea
- Abdominal pain
- Signs and symptoms of liver failure
- Many patients are asymptomatic

Laboratory Findings

- Elevated transaminases
- Alkaline phosphatase may be mildly elevated
- Viral serologies positive in viral hepatitis
- Autoimmune serologies usually positive in autoimmune hepatitis
- Other serologic tests, such as urinary copper, ceruloplasmin, serum α-1-antitrypsin, may be helpful

MICROSCOPIC

General Features

- Broad range of histologic appearances with some features in common
  - Portal inflammation
  - – Infiltrate consists primarily of lymphocytes
  - □ May have admixed plasma cells, histiocytes, and granulocytes

– Lymphoid follicles common in hepatitis C

– Nonspecific ductular reaction may be present at periphery of portal tract

- Lobular inflammation/necrosis
  - Necrosis may be mild and spotty or confluent and bridging
  - May be accompanied by ballooning degeneration, reactive hepatocellular changes
- Piecemeal necrosis (interface activity)
  - Defined as extension of inflammation into adjacent parenchyma with destruction of individual hepatocytes at interface
  - Results in ragged interface between portal tract and hepatic parenchyma
- Fibrosis

• Predominant pattern of inflammation in given case may be portal, periportal, lobular, or combination
  - Acute hepatitis usually diffusely involves lobule and is not confined to portal area

• Inflammatory process may be sporadically distributed within liver, resulting in sampling bias

Grading

• Grade 1 (minimal activity): Mild portal inflammation with scant piecemeal necrosis and no lobular necrosis

• Grade 2 (mild activity): Mild portal inflammation with piecemeal necrosis but scant lobular spotty necrosis

• Grade 3 (moderate activity): Moderate portal inflammation, piecemeal necrosis, spotty lobular necrosis

• Grade 4 (severe activity): Marked portal inflammation, brisk piecemeal necrosis, significant spotty lobular necrosis, areas of confluent necrosis resulting in bridging necrosis

Staging

• Stage 1 (portal fibrosis): Mild fibrous expansion of portal tracts

• Stage 2 (periportal fibrosis): Fine periportal strands of connective tissue with only rare portal-portal septa

• Stage 3 (septal or bridging fibrosis): Connective tissue bridges that link portal tracts to other portal tracts and to central veins

• Stage 4 (cirrhosis): Established bridging fibrosis with regenerative nodules

Histologic Patterns and Clinical Associations

• Predominantly portal-based hepatitis
  - Autoimmune hepatitis
  - Chronic hepatitis C
  - Nonspecific reactive hepatitis

• Predominantly periportal hepatitis
  - Autoimmune hepatitis
  - Chronic viral hepatitis
  - Drug-associated hepatitis

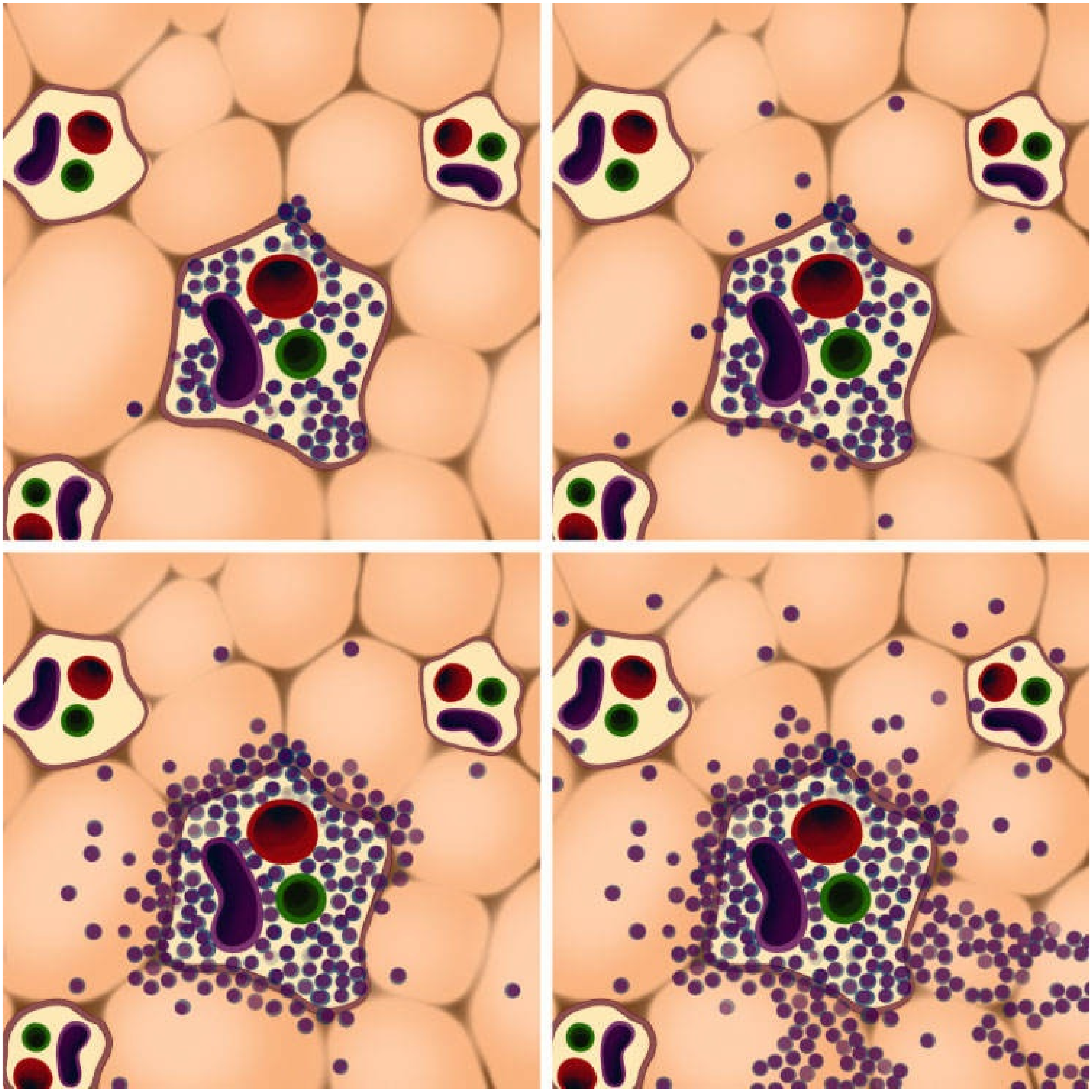
  - α-1-antitrypsin deficiency
  - Wilson disease
  - Nonspecific reactive hepatitis
- Predominantly lobular hepatitis
  - Acute viral hepatitis
  - Chronic or unresolved viral hepatitis
  - Autoimmune hepatitis
  - Drug-associated hepatitis
  - Nonspecific reactive hepatitis
- Some etiologies may occasionally have prominent cholestatic features
  - Acute or unresolved viral hepatitis
  - Autoimmune hepatitis
  - Drug-associated hepatitis

Differential Diagnoses

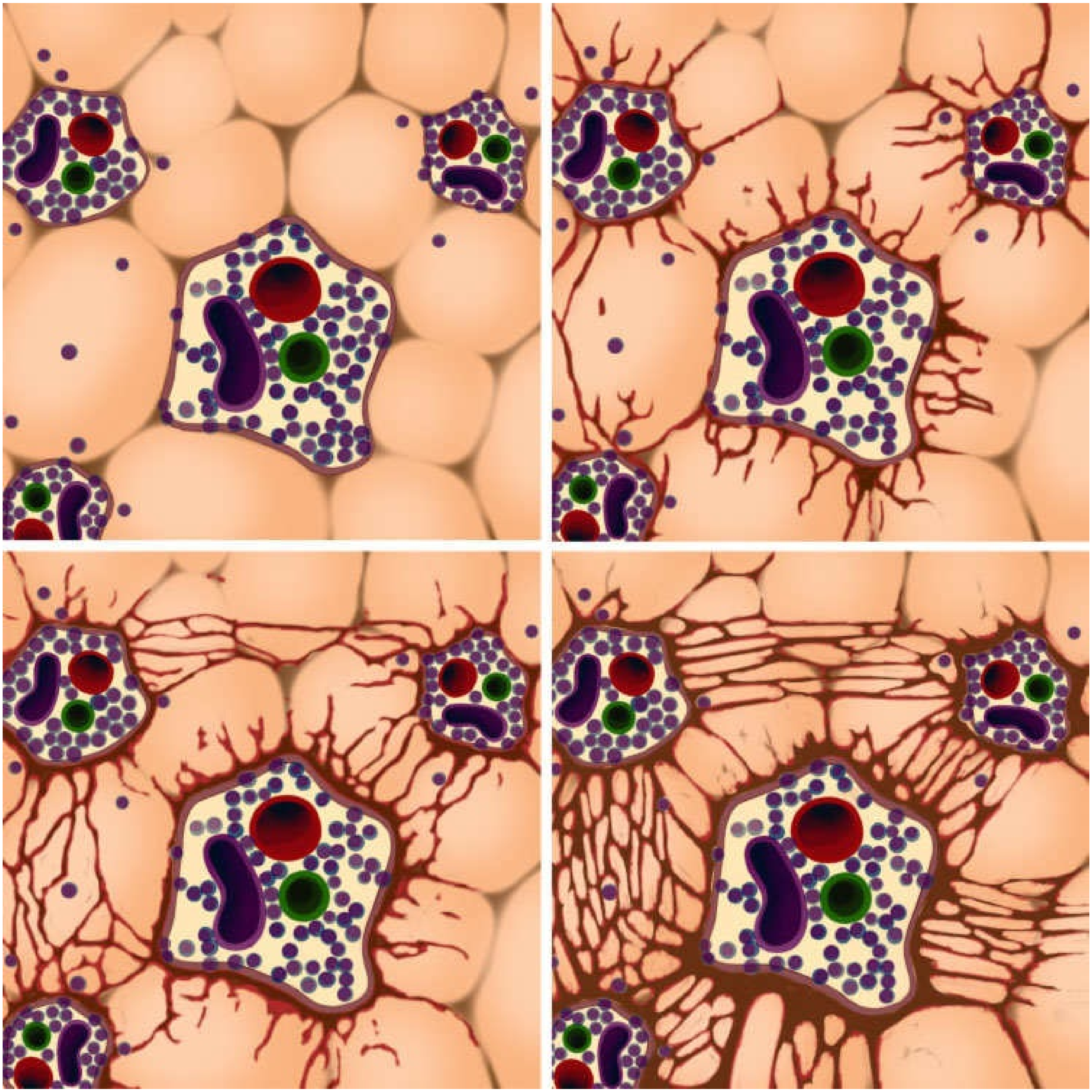
- Chronic biliary disease
  - Periportal copper deposition
  - Bile duct damage or loss
  - Elevation of alkaline phosphatase out of proportion to transaminases
  - Appropriate serologic studies &/or imaging studies may be helpful
- Large bile duct obstruction
  - Elevated alkaline phosphatase, GGT, and bilirubin
  - Usually lacks increased fibrosis
  - Neutrophils, portal edema may be prominent
  - Imaging studies helpful
- Lymphoma/leukemia
  - Infiltrates composed of atypical lymphocytes
  - Immunohistochemistry, gene rearrangement studies may be required
- Allograft rejection
  - History of liver transplant
  - Endothelialitis, lymphocytic cholangitis, duct damage are frequent features of rejection

Reporting

- Chronic hepatitis must be graded and staged in pathology report
  - “Chronic persistent” and “chronic active” hepatitis should no longer be used
- Comments regarding etiology, if possible

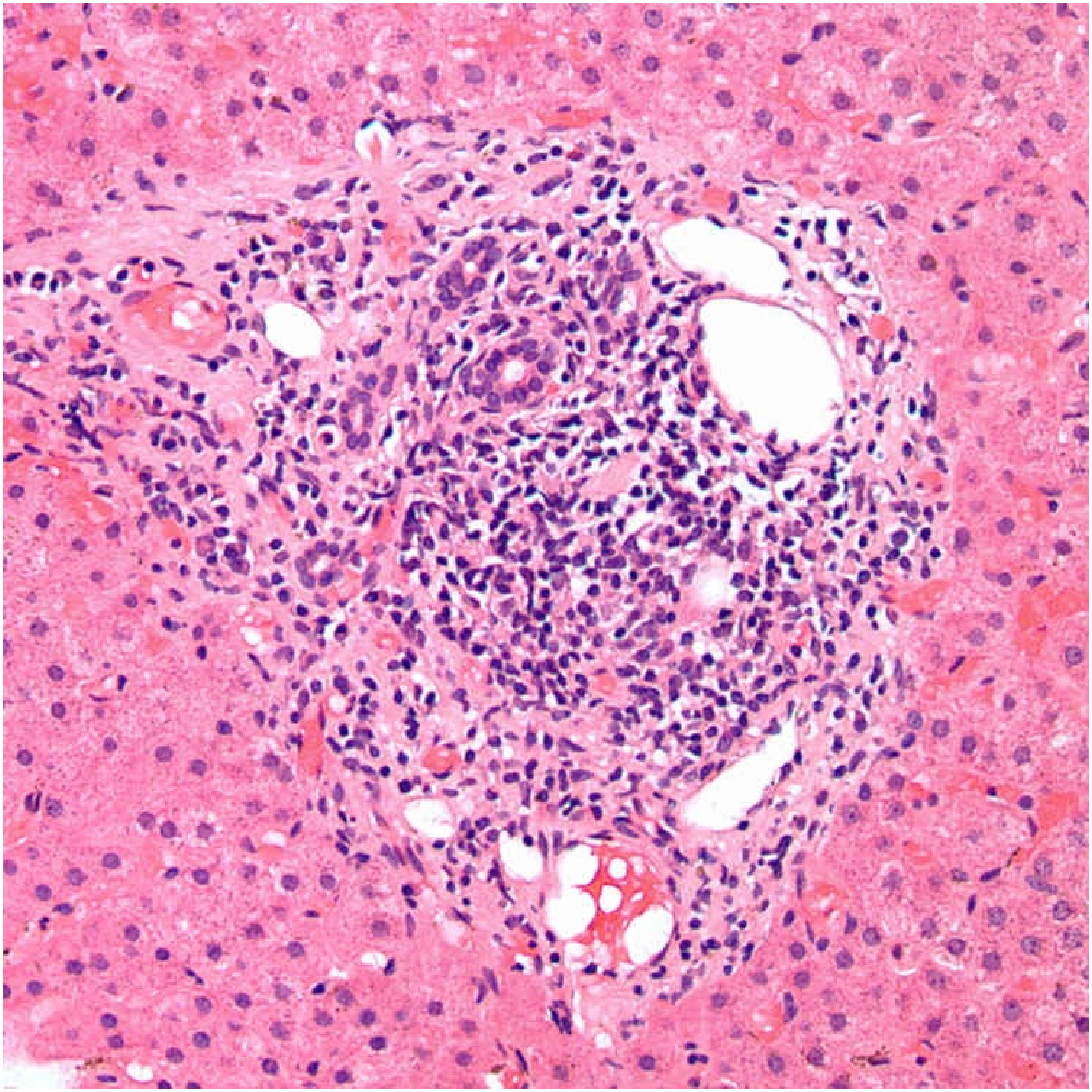


Grading of Chronic Hepatitis
This graphic illustrates the grading of chronic hepatitis. Upper left is minimal activity (grade 1), upper right is mild (grade 2), lower left is moderate (grade 3), and lower right is severe (grade 4).



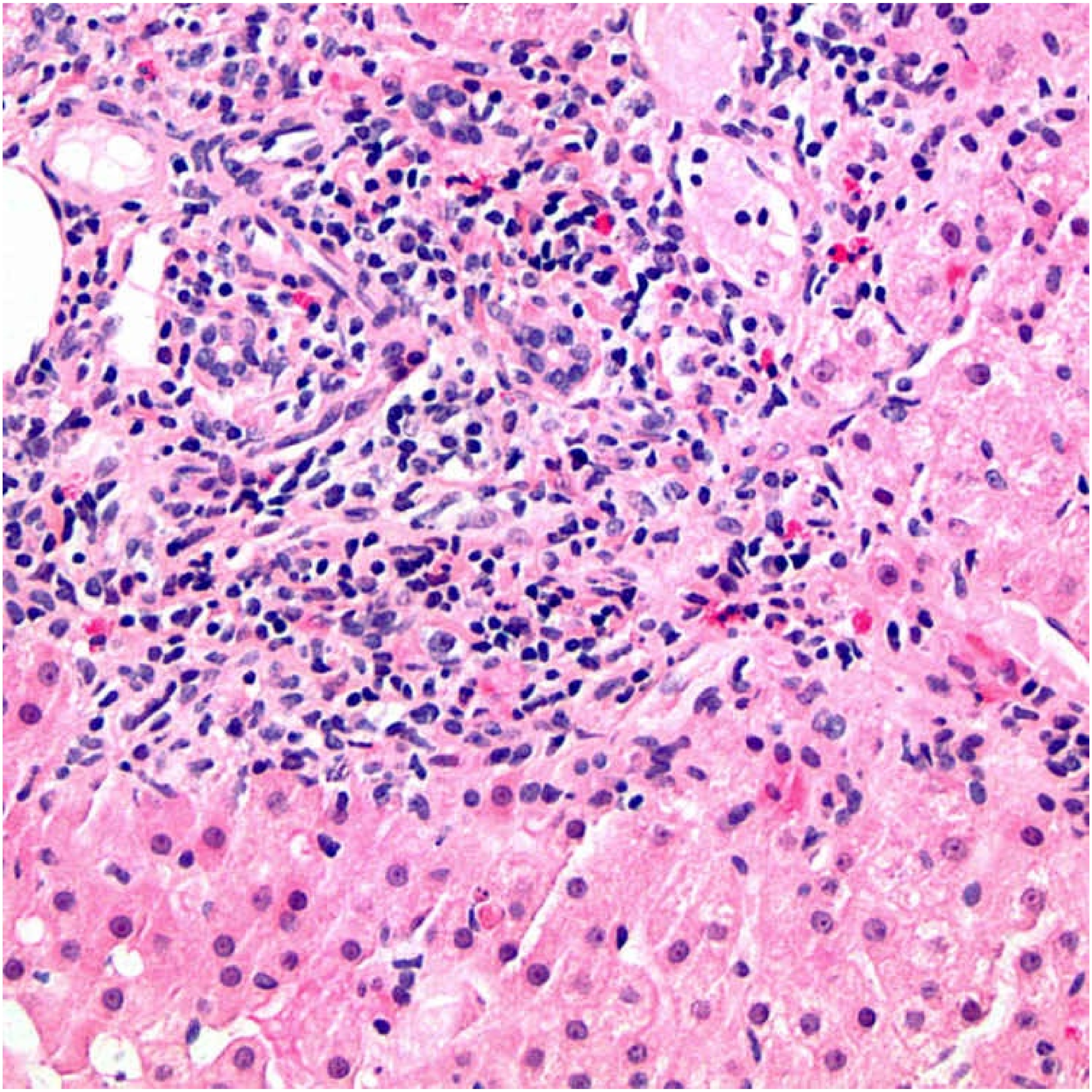
Staging of Fibrosis

This graphic illustrates staging of fibrosis. Upper left is portal fibrosis (stage 1), upper right is periportal (stage 2), lower left is bridging (stage 3), and lower right is cirrhosis (grade 4).



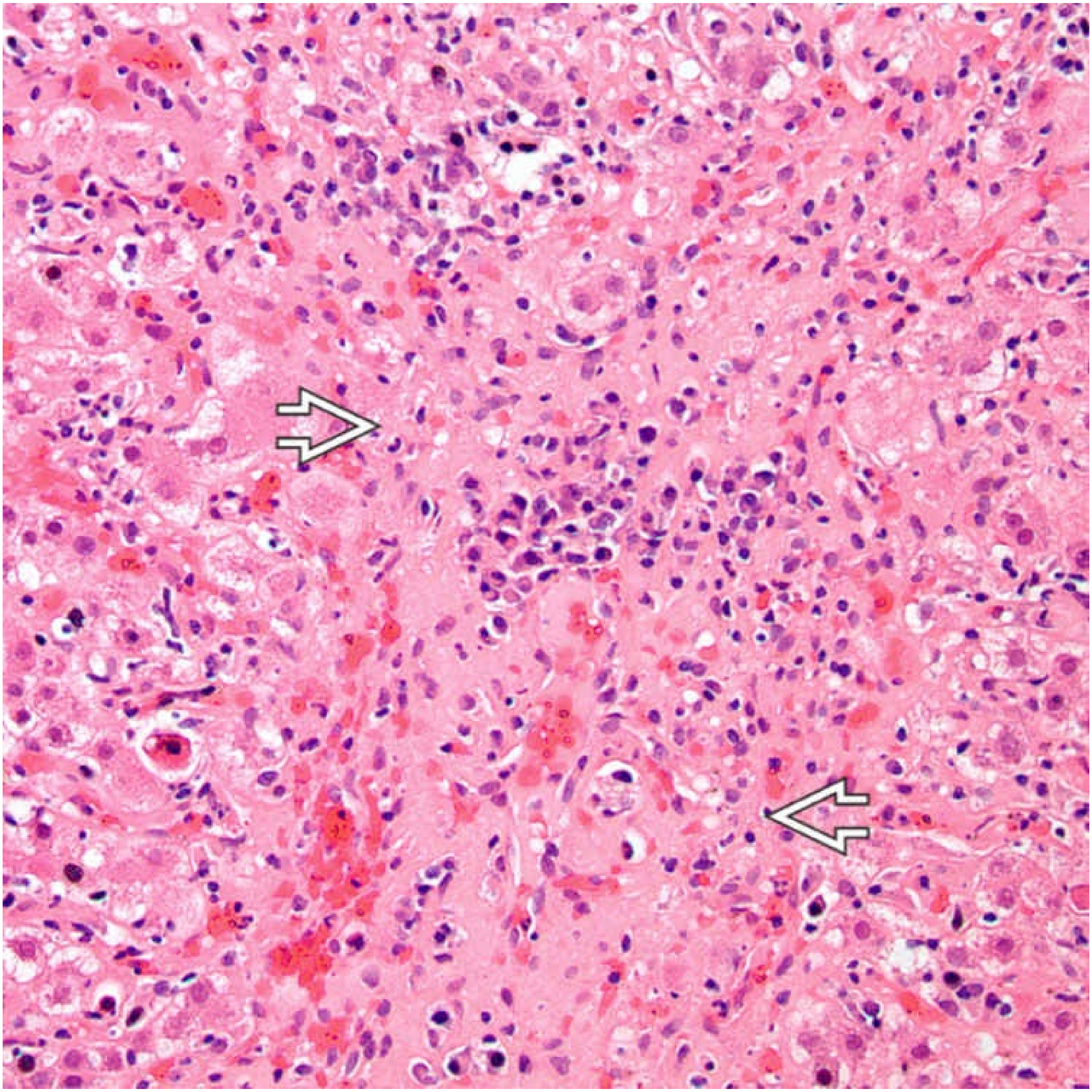
Grade 1

This case of hepatitis C shows minimal (grade 1) portal inflammation without piecemeal necrosis or significant lobular activity.

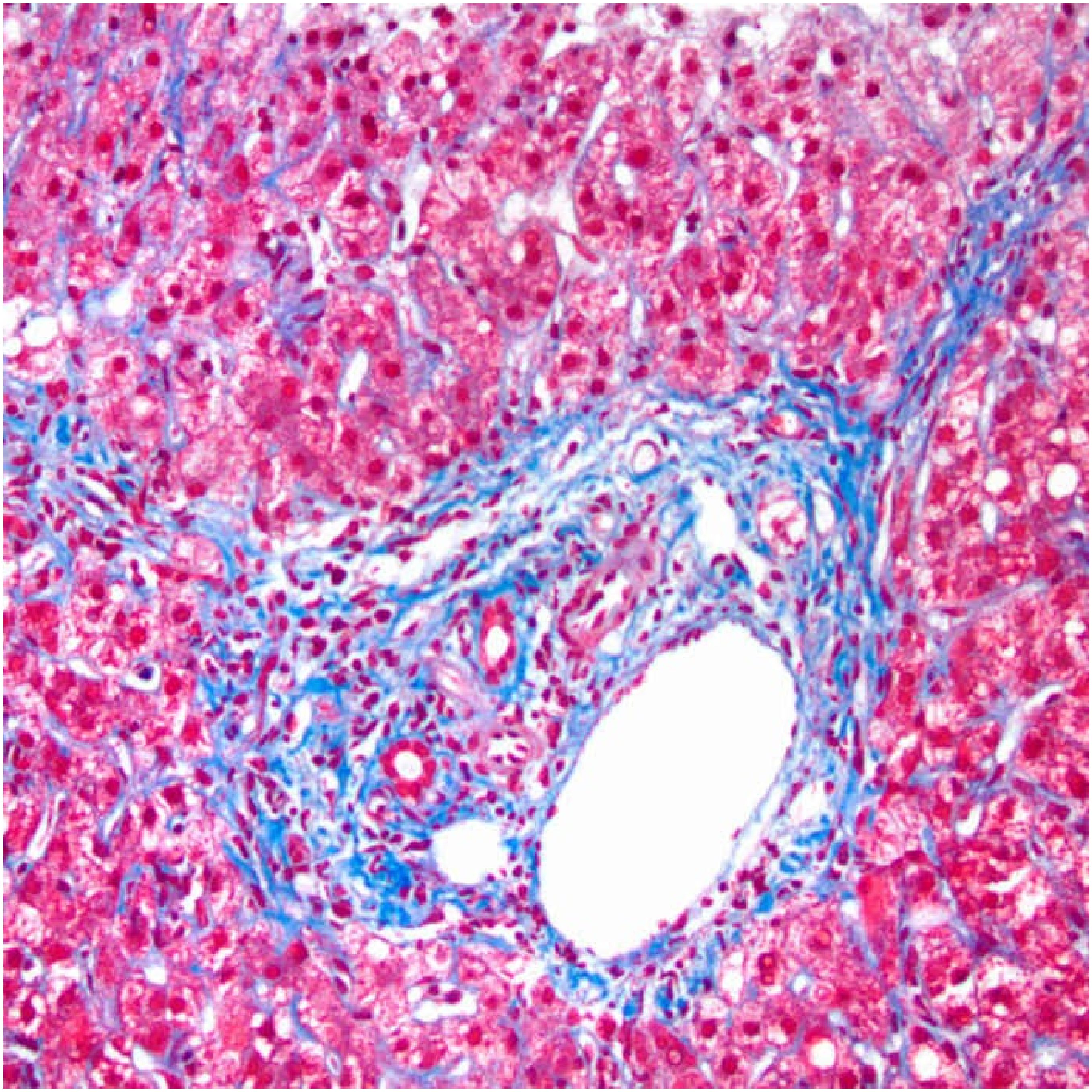


Grade 3

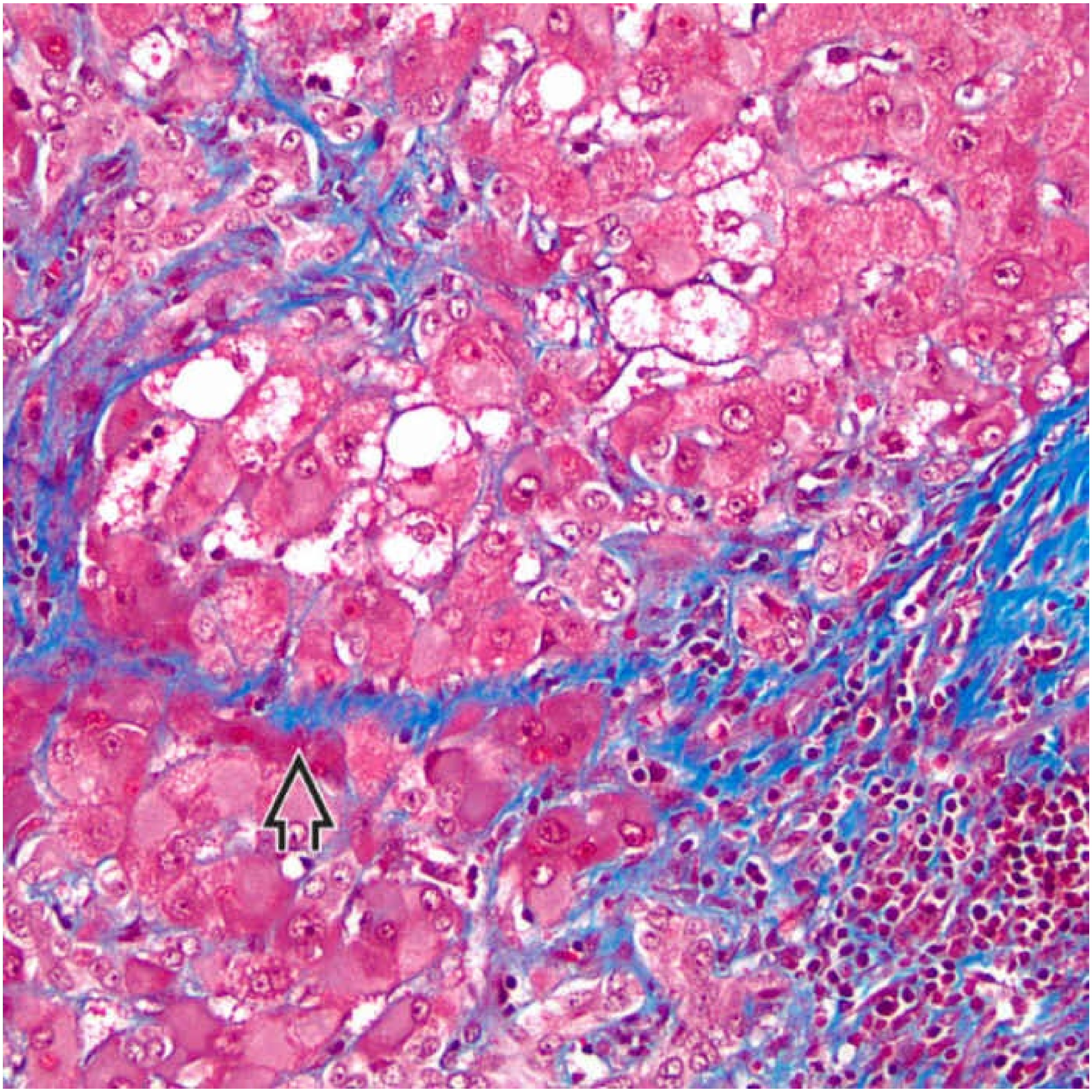
This case of hepatitis C shows moderate portal inflammation and piecemeal necrosis. Spotty lobular necrosis was also seen in the biopsy, making this a grade 3 lesion.



Bridging Necrosis (Grade 4)
This case of autoimmune hepatitis shows bridging necrosis ⇨, a hallmark of severe (grade 4) activity.
Note the numerous plasma cells.

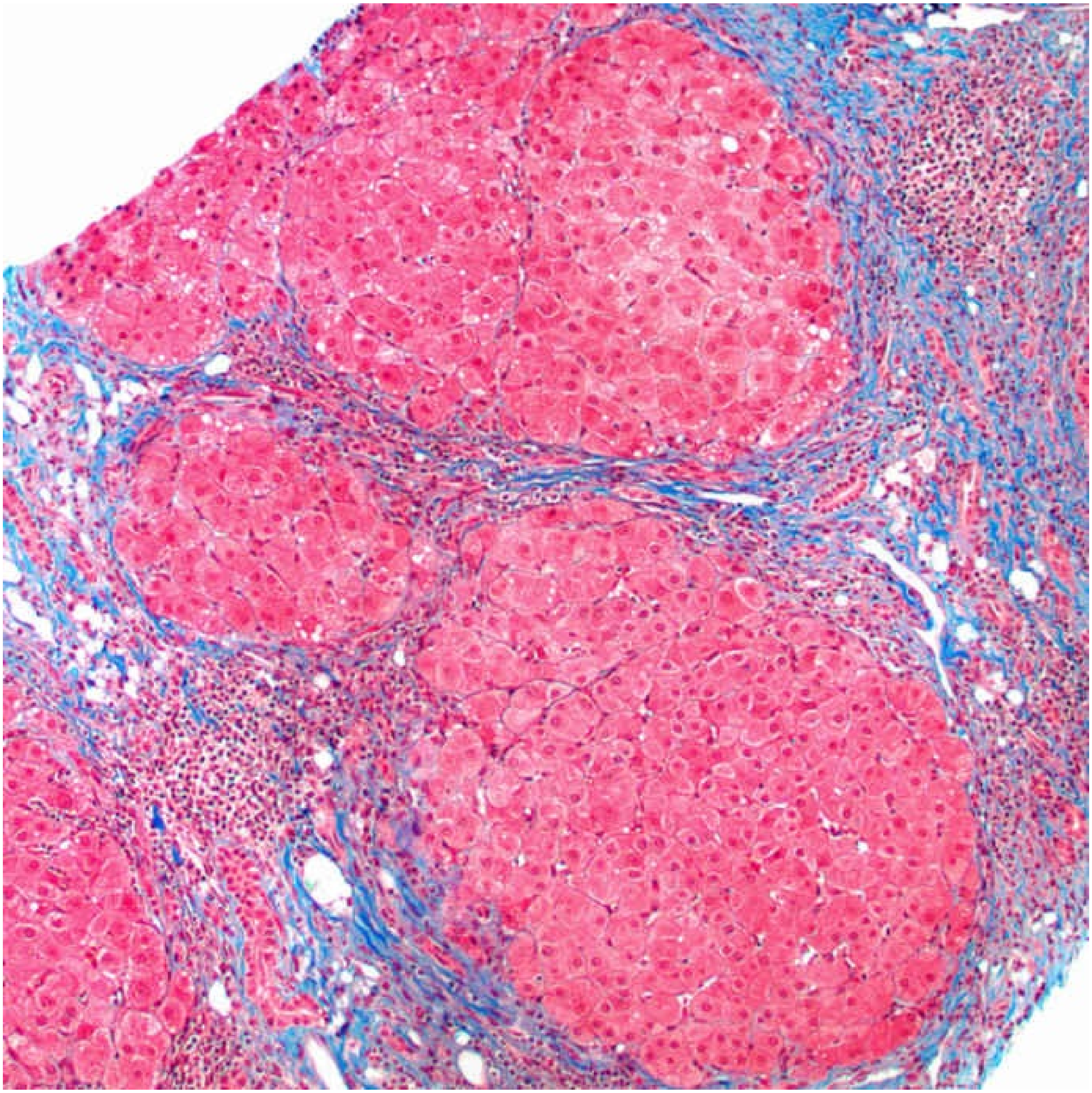


Stage 2 Fibrosis
Stage 2 (periportal) fibrosis features fine strands of periportal connective tissue. Rare portal-portal septa may be present at this stage.

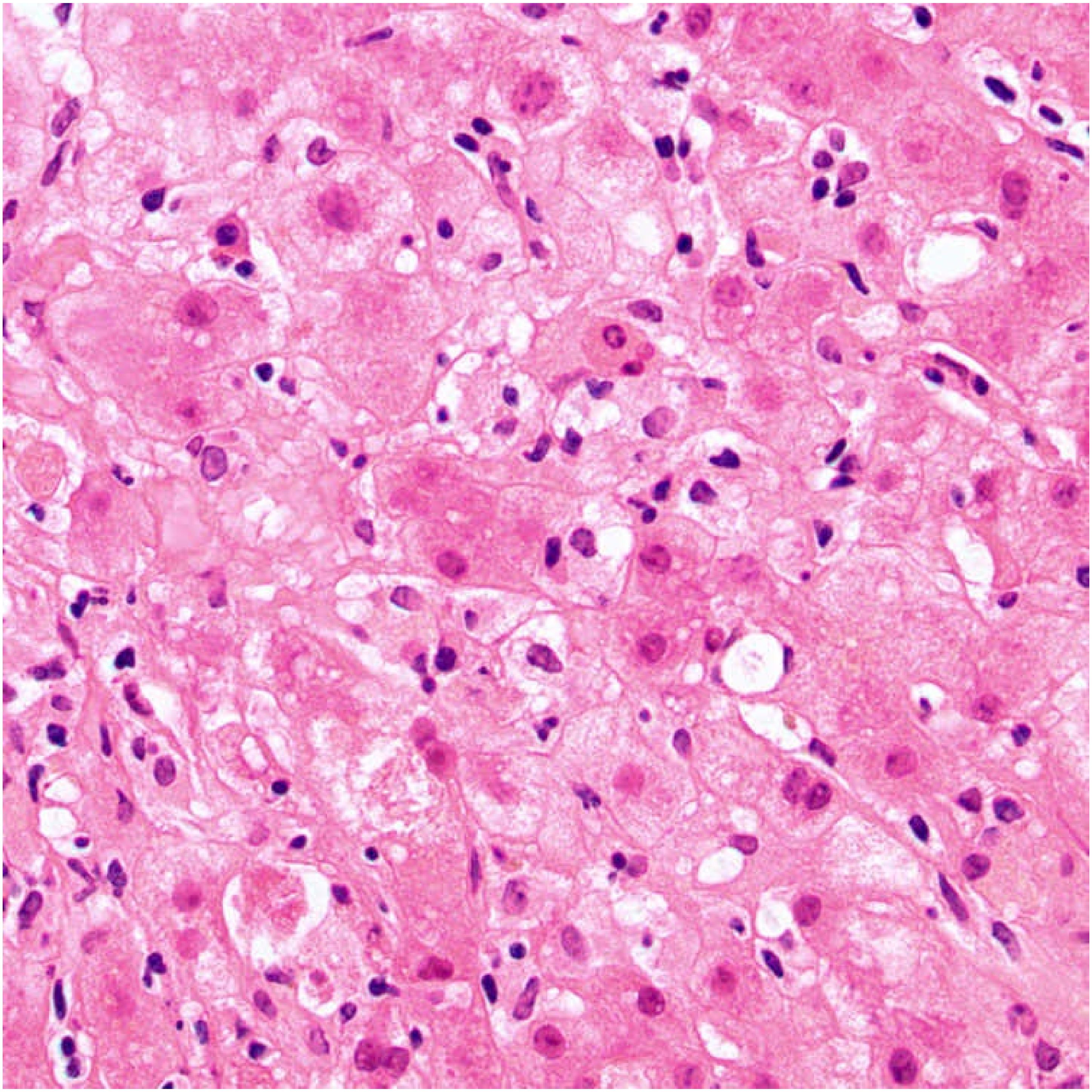


Stage 3 Fibrosis

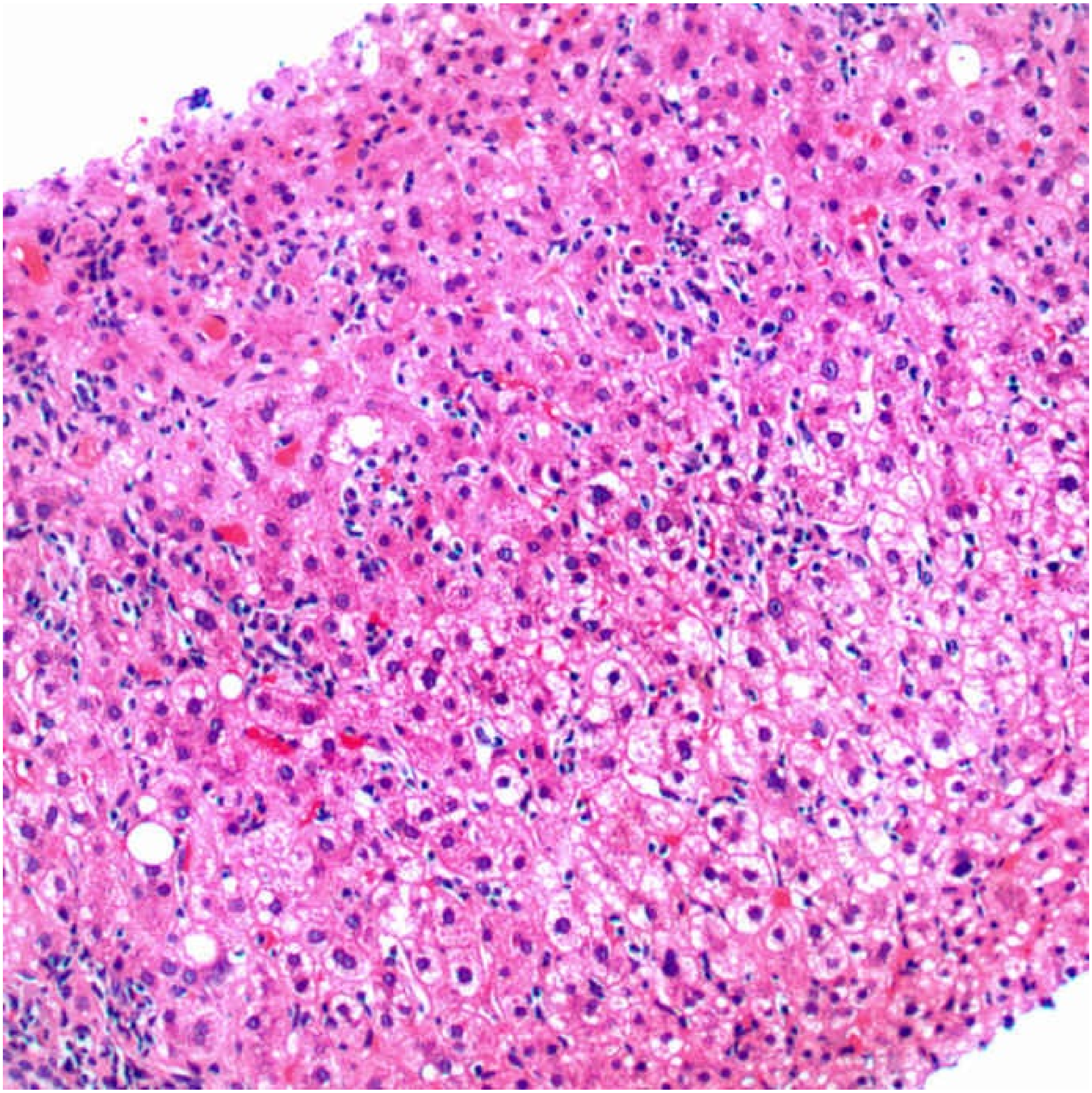
Bridging or septal fibrosis (stage 3) consists of connective tissue bridges ➩ that link portal tracts to each other or to central veins. Architecture may be mildly distorted, but there are no regenerative nodules.



Cirrhosis (Stage 4 Fibrosis)
Cirrhosis (stage 4 fibrosis) consists of established bridging fibrosis and regenerative nodules.

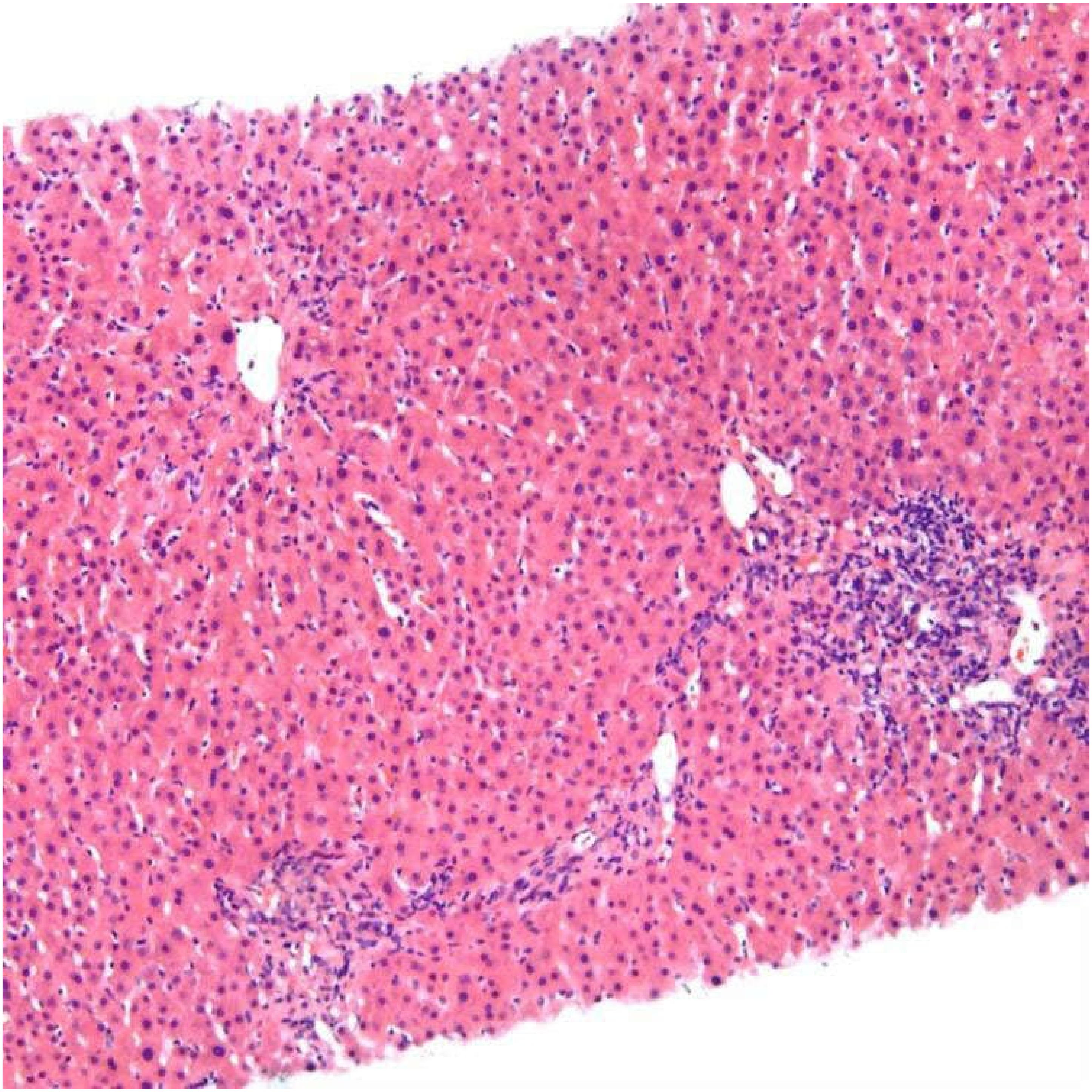


Acute Viral Hepatitis
This case of acute viral hepatitis shows a mild lobular lymphocytic infiltrate along with increased Kupffer cells and reactive hepatocellular changes.

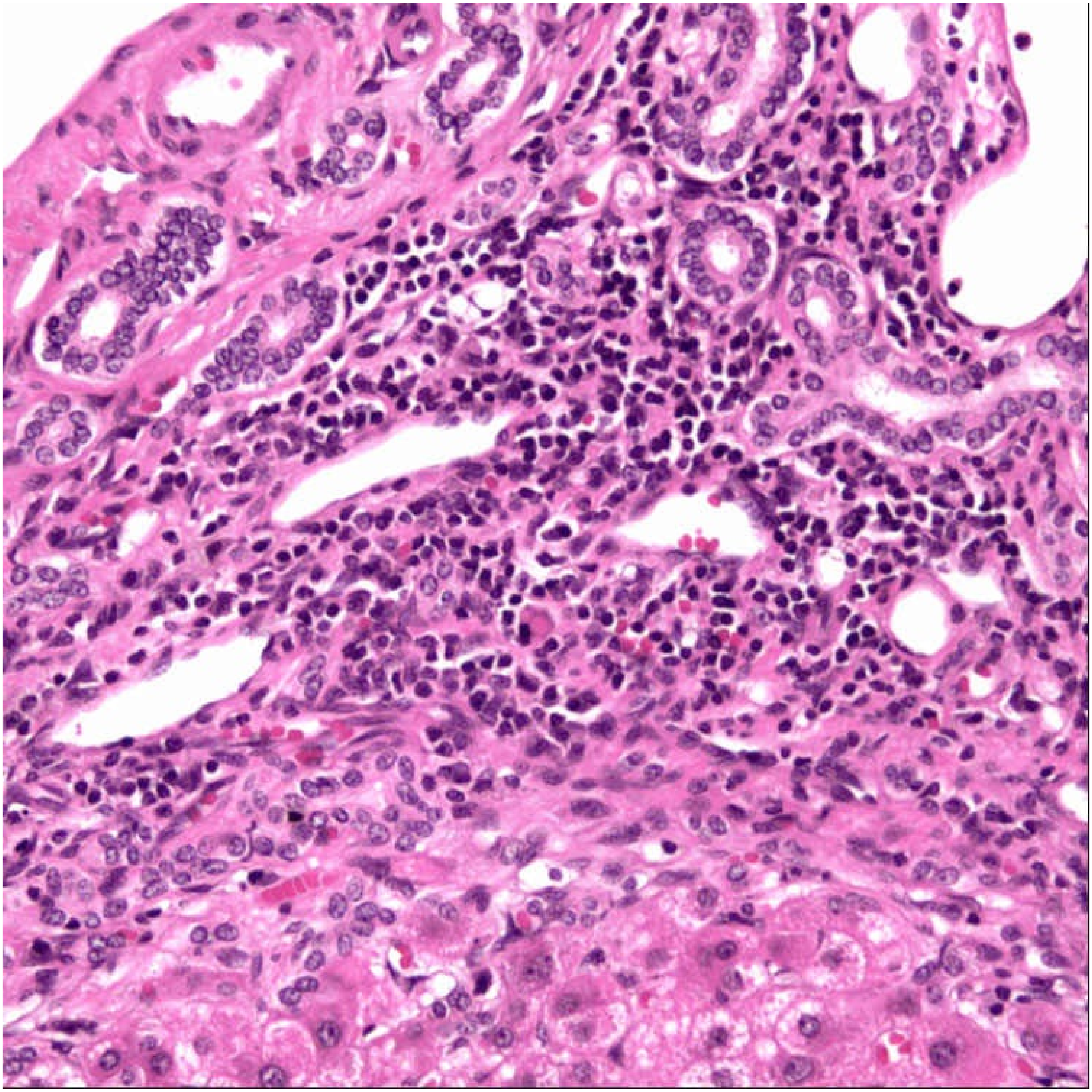


Lobular Hepatitis

A more severe lobular hepatitis is seen in this case of autoimmune hepatitis, featuring a marked lymphocytic infiltrate with hepatocyte necrosis and lobular disarray.

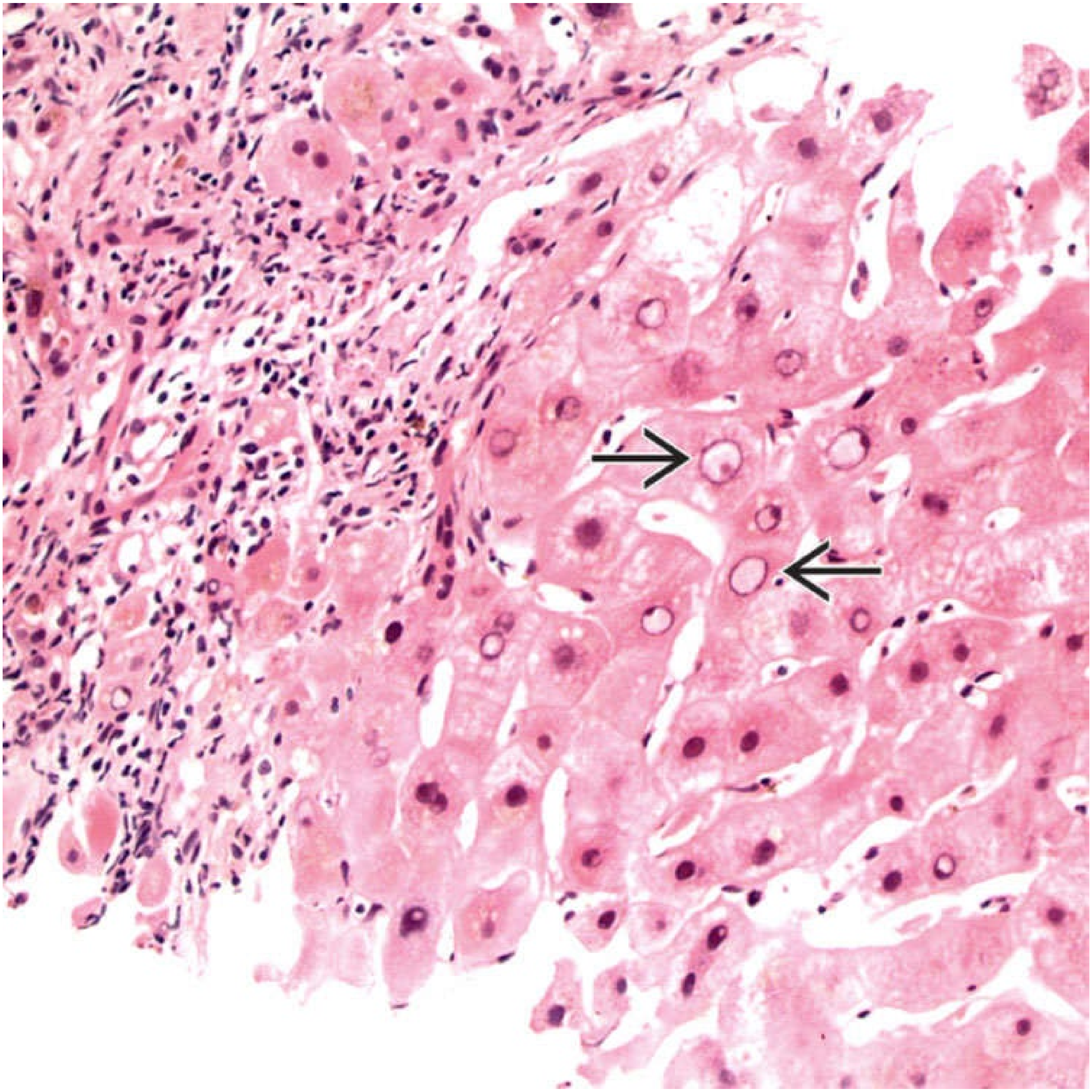


Adverse Drug Reaction
This case of an adverse drug reaction to propylthiouracil features both portal and lobular hepatitis. Trichrome stain showed no significant increase in fibrosis.



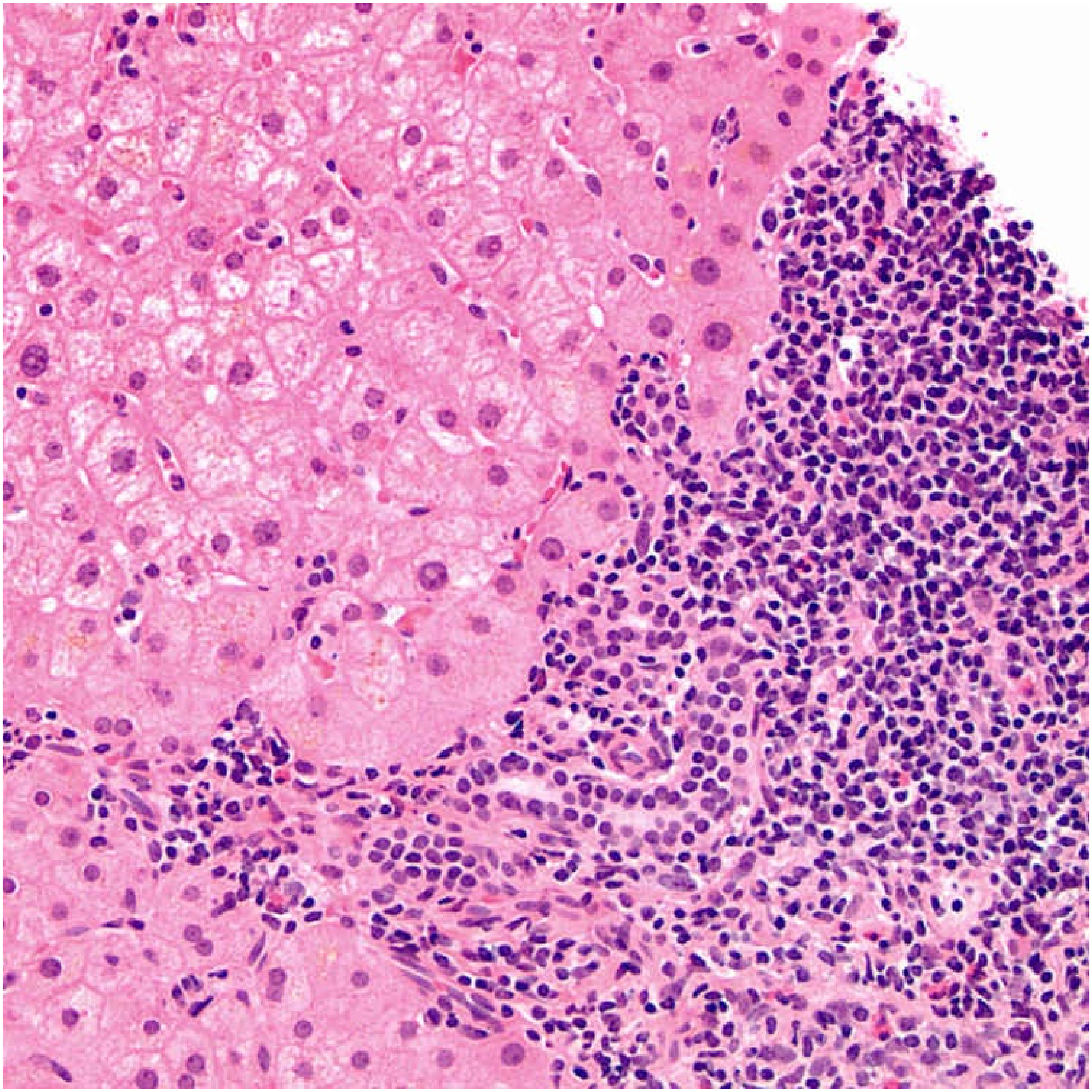
α-1-Antitrypsin Deficiency

This case of α-1-antitrypsin deficiency shows a chronic, hepatitis-like pattern featuring a portal/periportal lymphocytic infiltrate with cholangiolar proliferation. PAS/diastase helps to distinguish this nonspecific inflammatory pattern from other causes of hepatitis by highlighting the globules within hepatocytes.

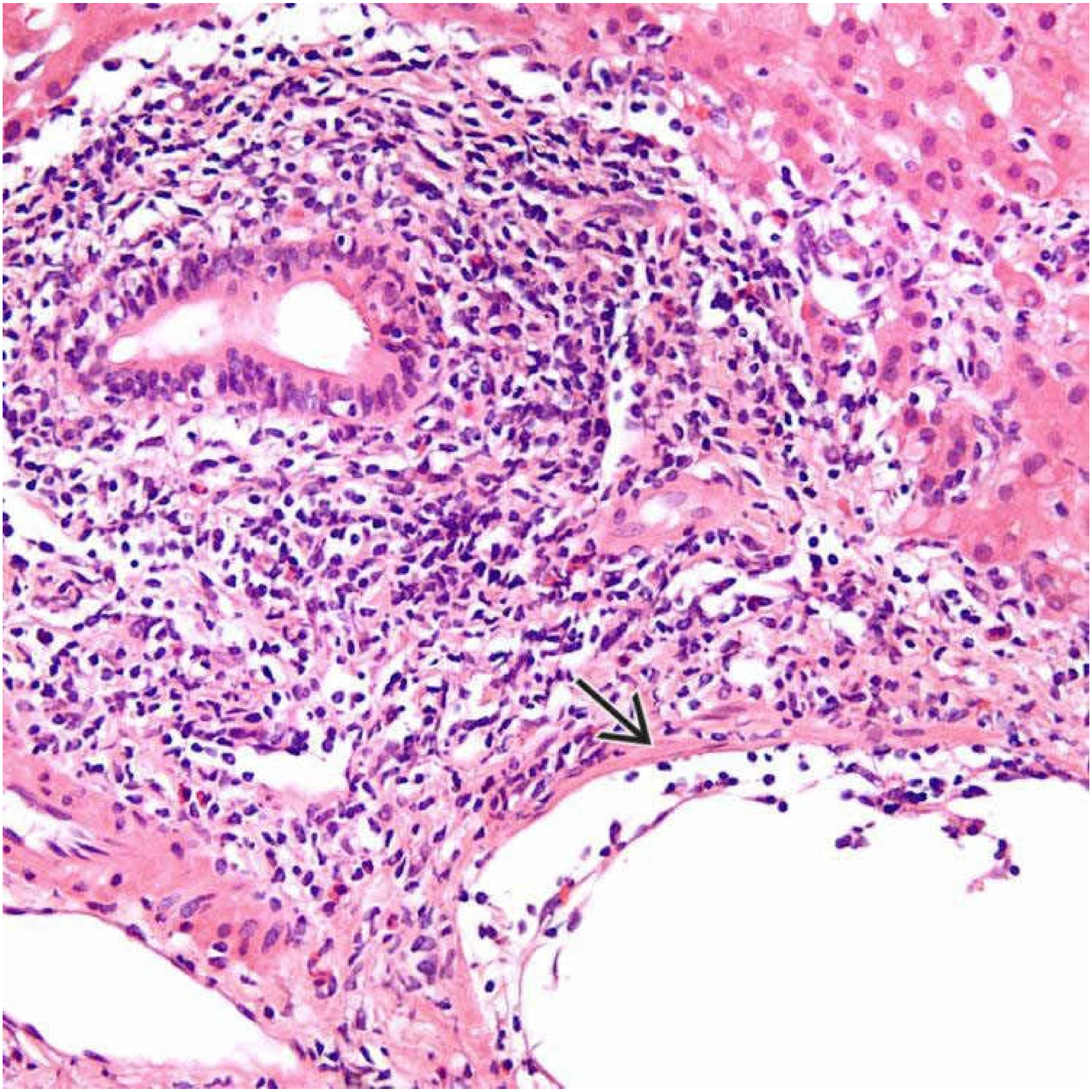


Wilson Disease

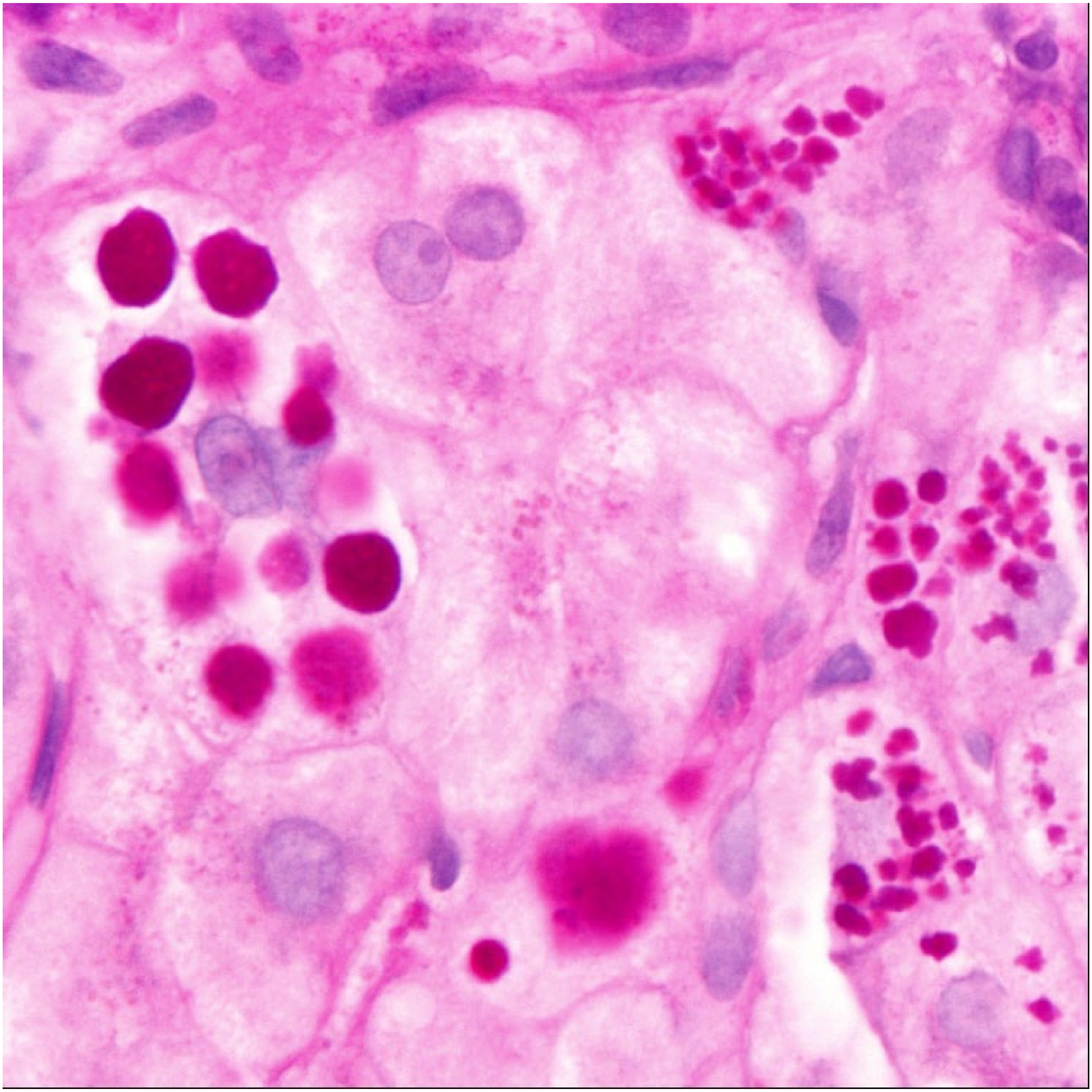
This case of Wilson disease shows a portal and periportal lymphocytic infiltrate. Note the prominent glycogenated nuclei →.



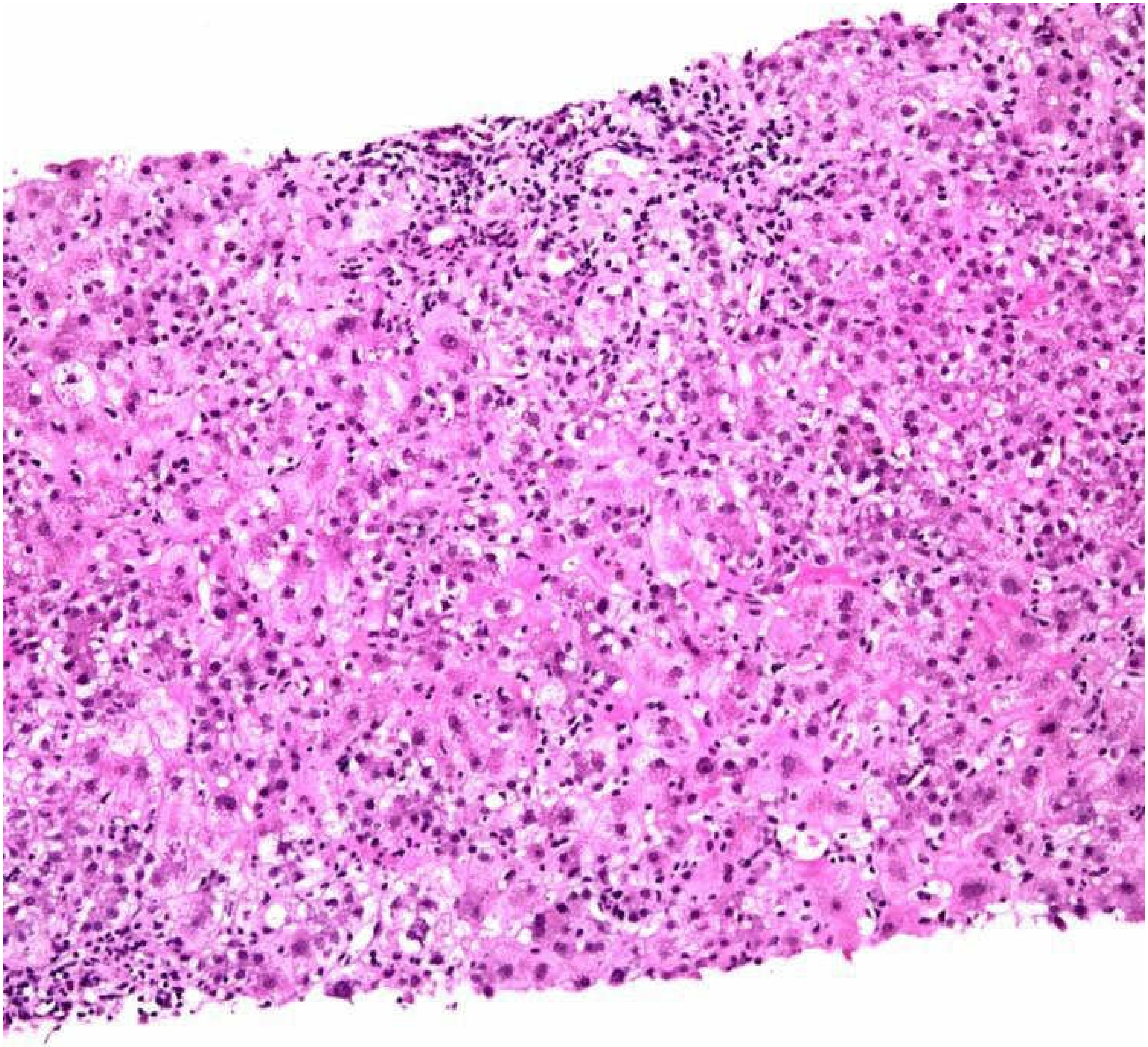
Primary Biliary Cholangitis
This case of primary biliary cholangitis shows portal-based inflammation without florid duct lesions, mimicking chronic hepatitis of other causes.



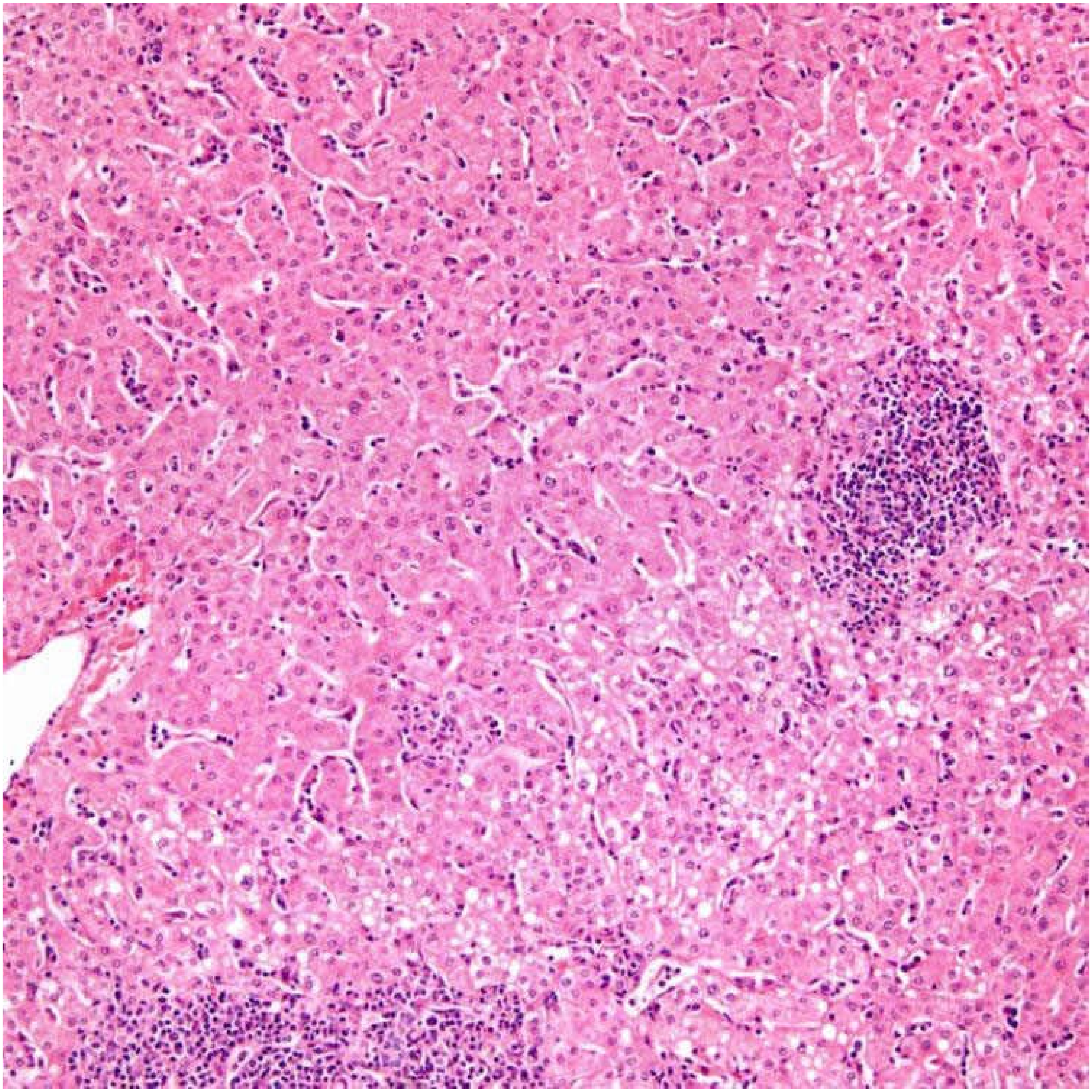
The portal inflammation in acute rejection can mimic hepatitis of other causes. The lymphocytic cholangitis and well-developed endothelialitis → help to diagnose rejection.



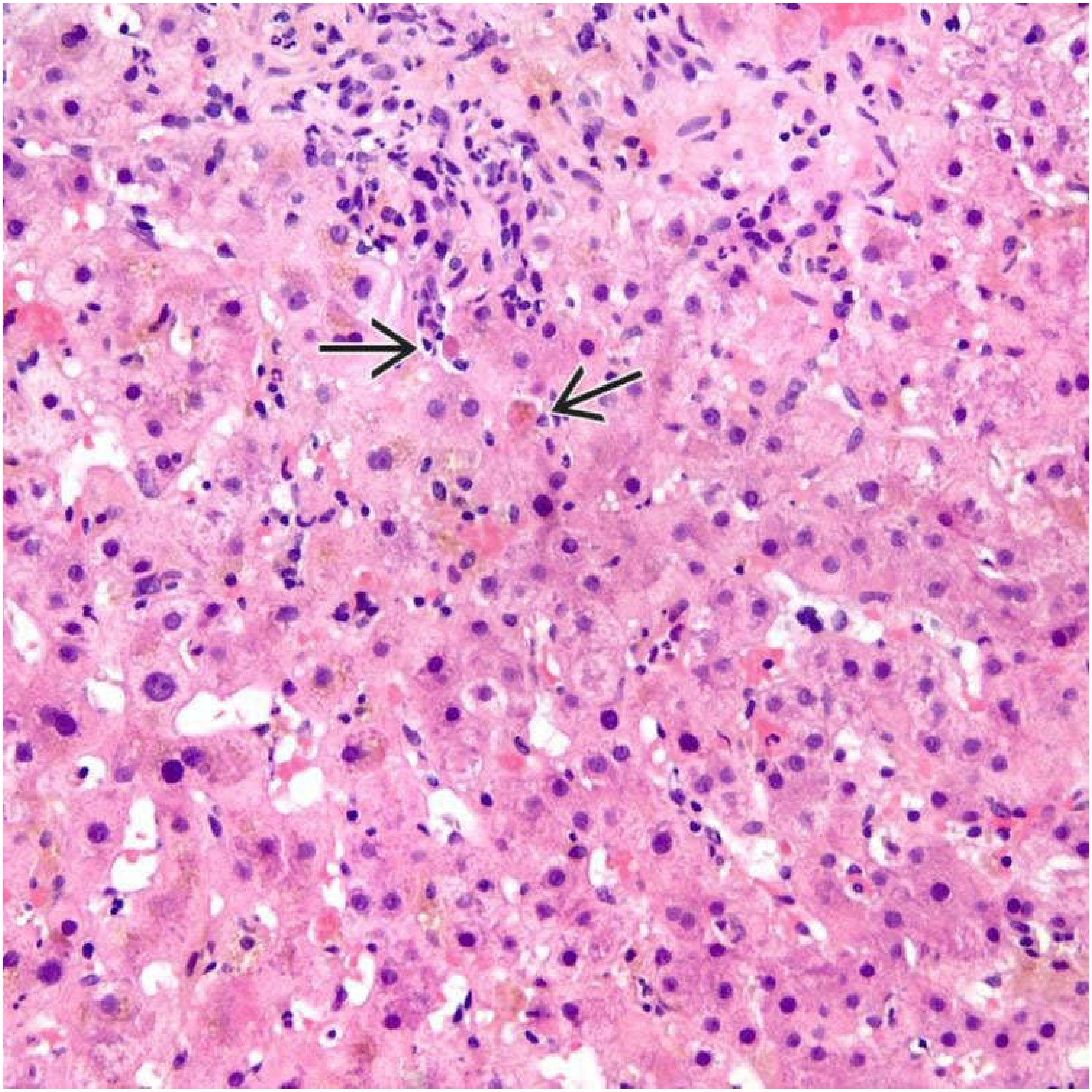
This PAS with diastase demonstrated PAS(+), diastase-resistant globules in the periportal region in this case of α-1-antitrypsin deficiency.



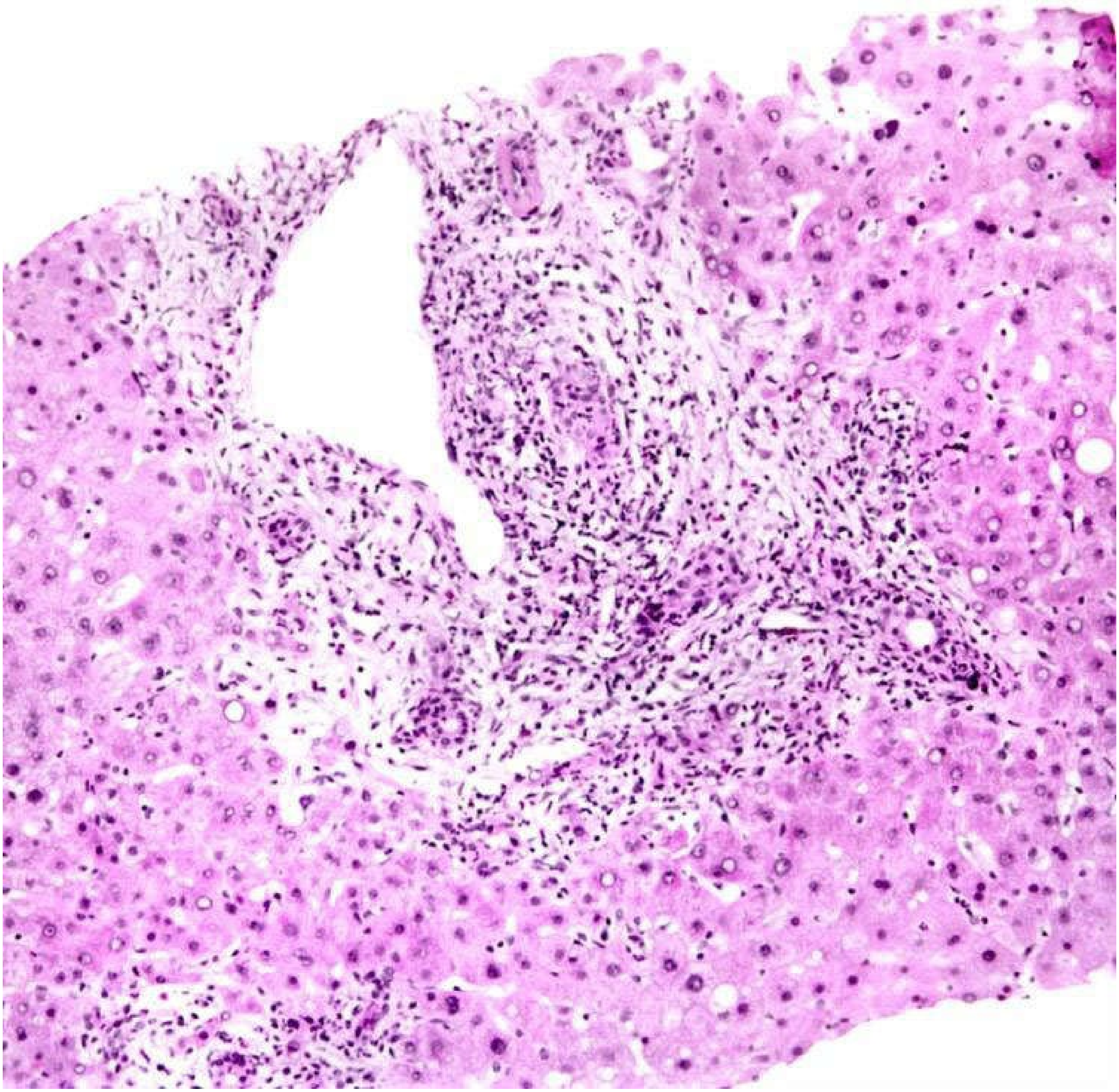
This case of autoimmune hepatitis shows marked lobular hepatitis with feathery degeneration of hepatocytes, apoptotic hepatocytes, and reactive hepatocellular changes. These features together are known as lobular disarray.



This case of Epstein-Barr virus hepatitis shows portal inflammation as well as a sinusoidal lymphocytosis.



This case of acute hepatitis B shows primarily lobular inflammation composed of lymphocytes and histiocytes. Scattered apoptotic hepatocytes are also seen →.


Portal edema, neutrophils, and ductular reaction help to distinguish large bile duct obstruction from other causes of acute and chronic hepatitis.

SELECTED REFERENCES

1. Lefkowitch, JH. Liver biopsy assessment in chronic hepatitis. *Arch Med Res*. 2007; 38(6):634–643.
2. Theise, ND. Liver biopsy assessment in chronic viral hepatitis: a personal, practical approach. *Mod Pathol*. 2007; 20(Suppl 1):S3–14.
3. Scheuer, PJ. Liver biopsy size matters in chronic hepatitis: bigger is better. *Hepatology*. 2003; 38(6):1356–1358.
4. Batts, KP, et al. Chronic hepatitis. an update on terminology and reporting. *Am J Surg Pathol*. 1995; 19(12):1409–1417.

5. Burgart, LJ, et al. Recent-onset autoimmune hepatitis. Biopsy findings and clinical correlations. *Am J Surg Pathol*. 1995; 19(6):699–708.
6. Desmet, VJ, et al. Classification of chronic hepatitis: diagnosis, grading and staging. *Hepatology*. 1994; 19(6):1513–1520.
7. Lefkowitch, JH, et al. Pathological diagnosis of chronic hepatitis C: a multicenter comparative study with chronic hepatitis B. The Hepatitis Interventional Therapy Group. *Gastroenterology*. 1993; 104(2):595–603.
8. Scheuer, PJ, et al. The pathology of hepatitis C. *Hepatology*. 1992; 15(4):567–571.
9. Schlichting, P, et al. Liver biopsy in chronic aggressive hepatitis. Diagnostic reproducibility in relation to size of specimen. *Scand J Gastroenterol*. 1983; 18(1):27–32.
10. Peters, RL. Viral hepatitis: a pathologic spectrum. *Am J Med Sci*. 1975; 270(1):17–31.
11. Popper, H, et al. The vocabulary of chronic hepatitis. *N Engl J Med*. 1971; 284(20):1154–1156.

Acute Viral Hepatitis

KEY FACTS

Terminology

- Hepatocyte necrosis and inflammation resulting from acute viral infection

Etiology/Pathogenesis

- Hepatitis A and hepatitis B virus infection accounts for vast majority of acute viral hepatitis cases in USA
  - Hepatitis C accounts for ~ 20% of cases of acute hepatitis

Clinical Issues

- Symptoms generally mild or patients are asymptomatic
  - Fulminant hepatic failure is rare
- Most patients with acute hepatitis A virus infection fully recover within 2 months of disease onset
  - No specific drug therapy available for acute hepatitis A virus infection
- Laboratory values
  - Elevated transaminases at 5-10x normal values
  - Viral serologies often helpful
- Supportive care is mainstay of treatment for patients with acute hepatitis A or acute hepatitis E
  - Drug therapy (antivirals or immune modulators) may be useful in acute hepatitis B and C

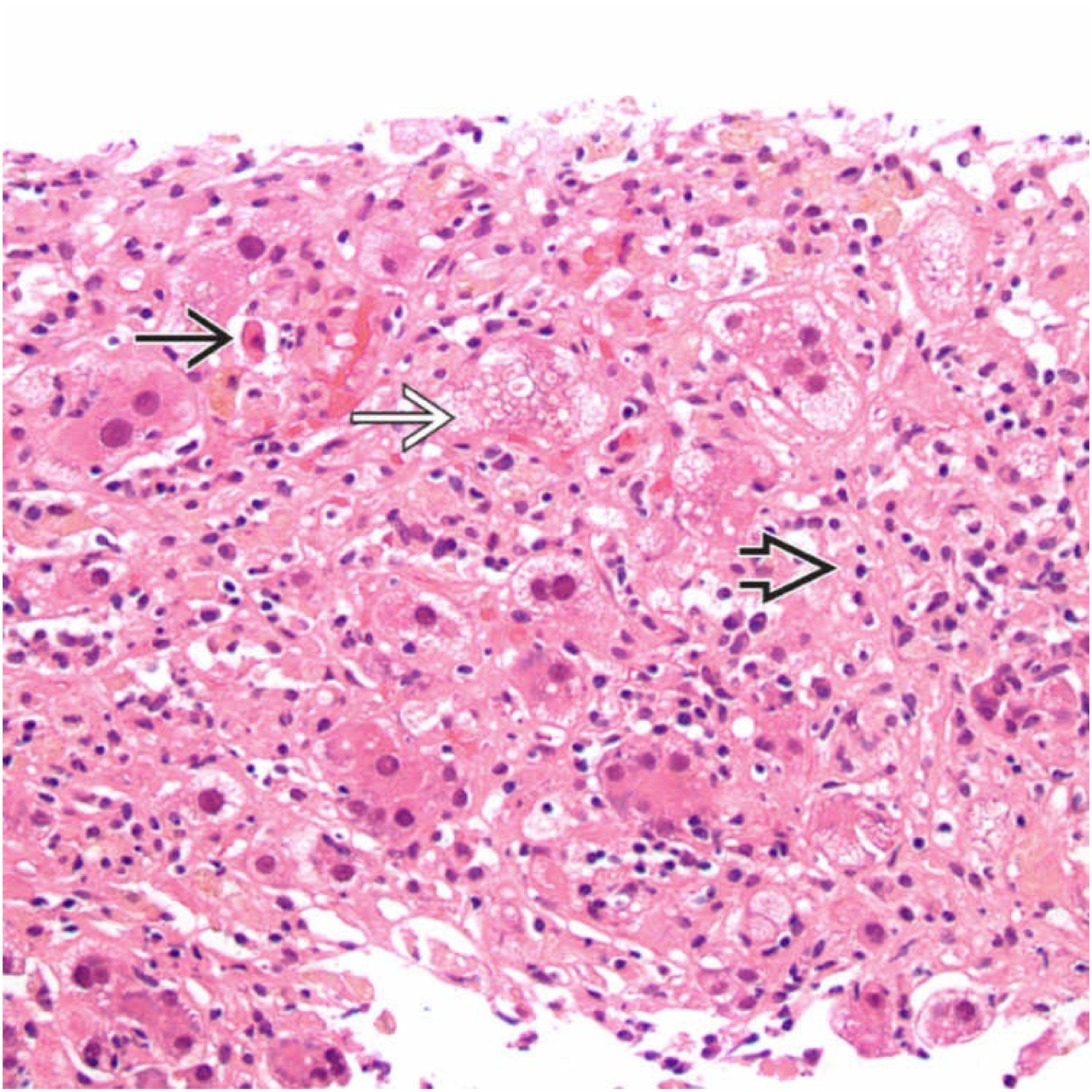
Microscopic

- Lobular disarray characterized by diffuse lobular inflammation and hepatocyte swelling, necrosis, and regeneration
- May see mild portal and periportal inflammation, particularly in acute hepatitis A virus infection

Diagnostic Checklist

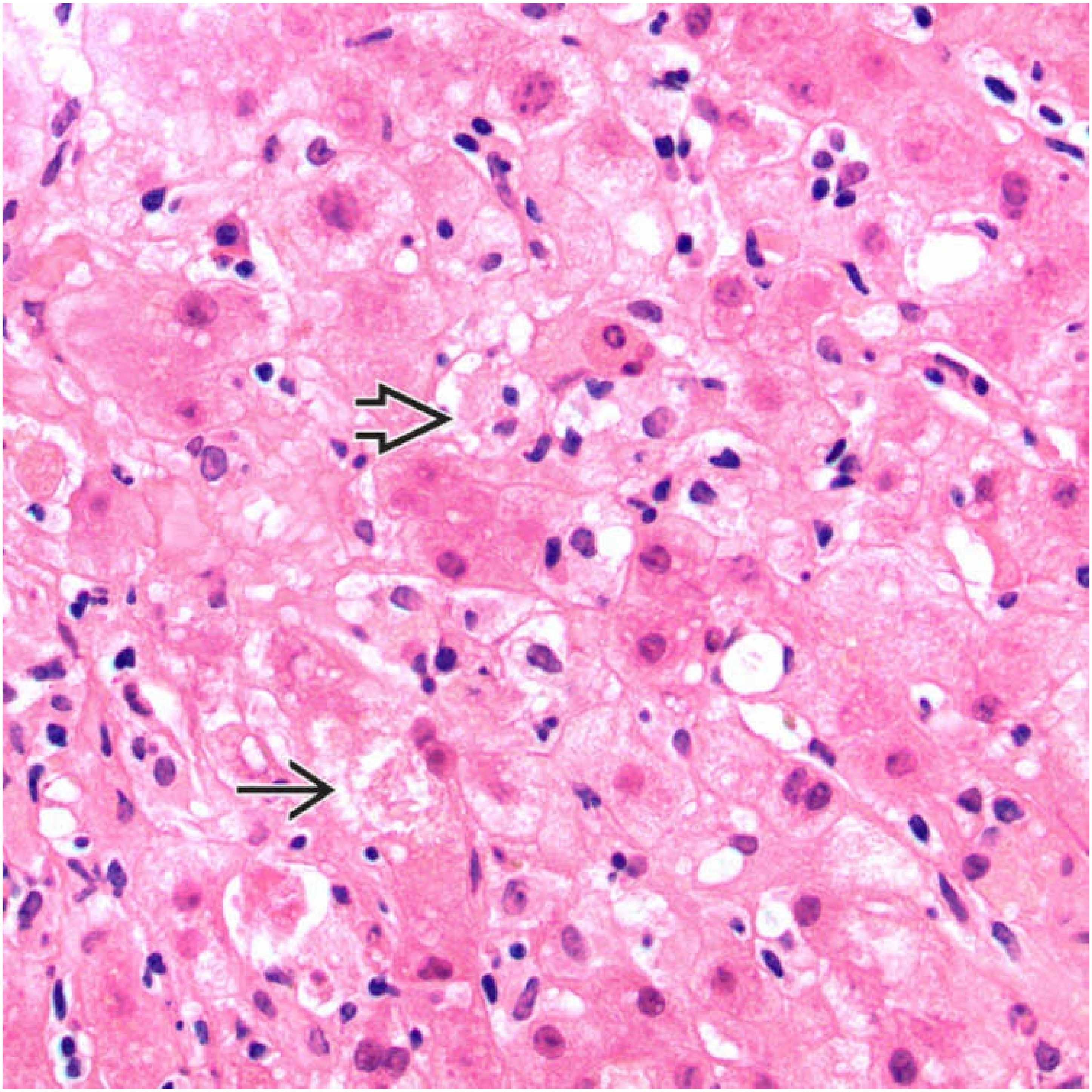
- Lobular inflammation and injury exceed portal inflammation

• Usually recognized clinically, so liver biopsy seldom performed

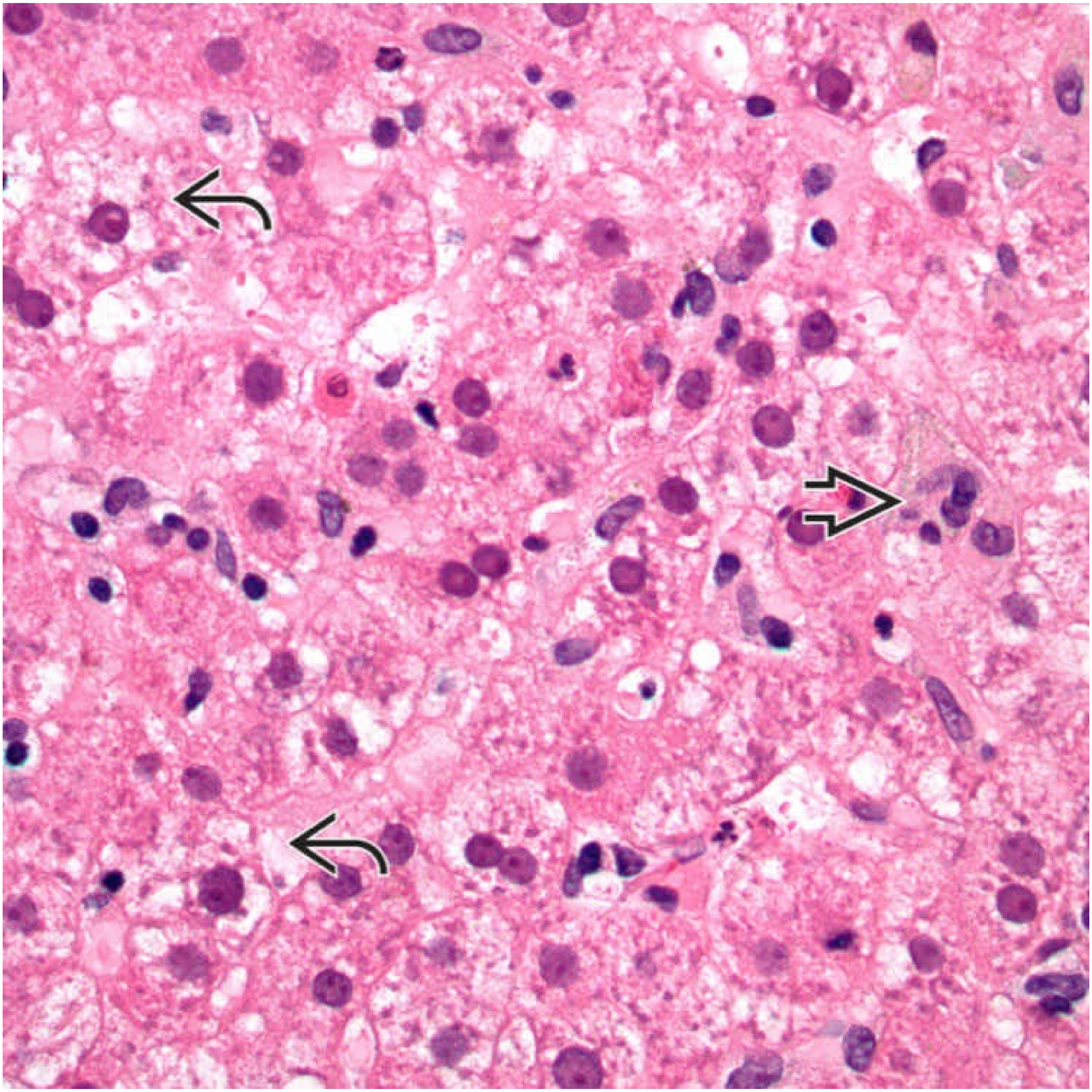


Lobular Disarray

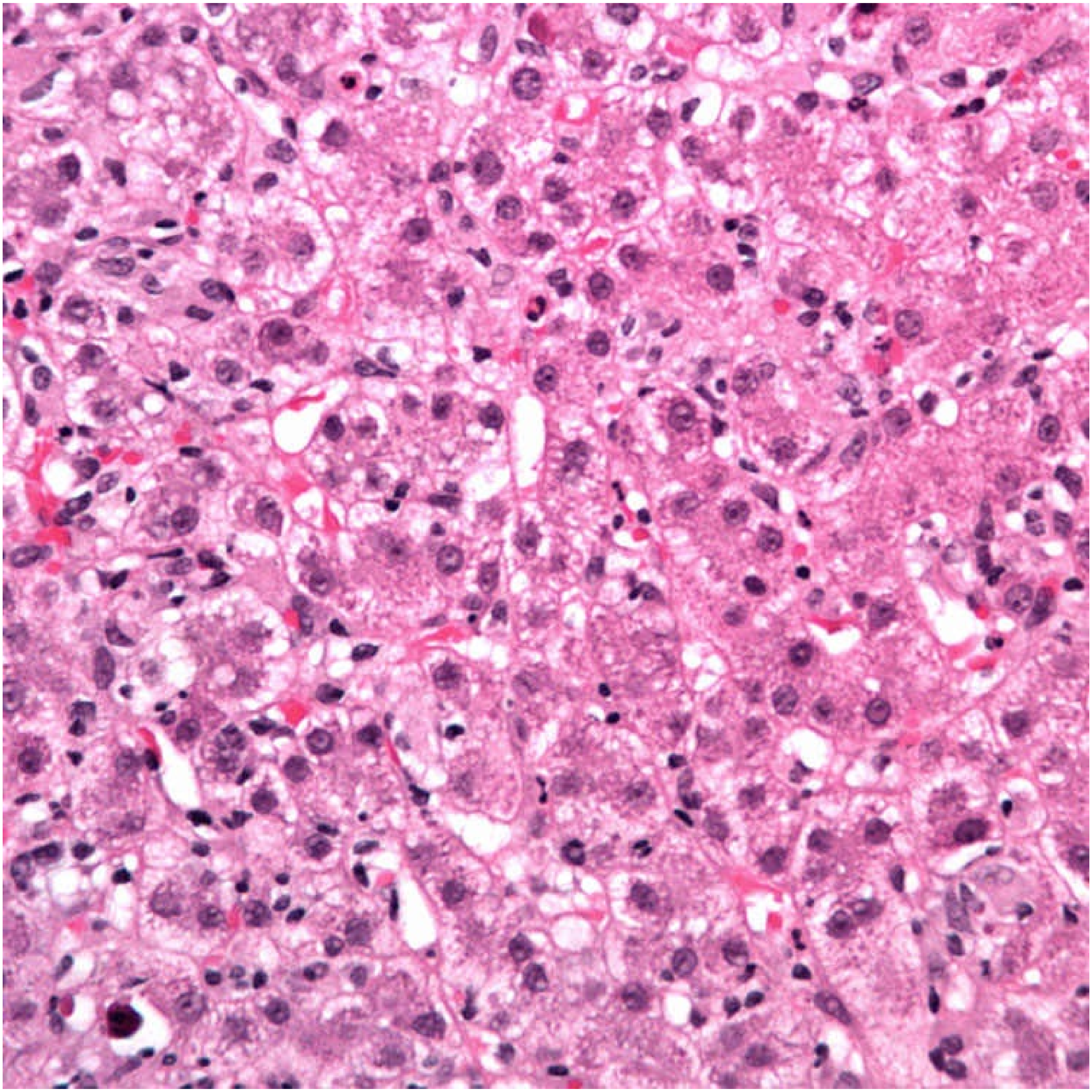
This biopsy shows diffuse lobular disarray characterized by hepatocyte swelling ⇒, single-cell necrosis →, and areas of hepatocyte dropout ⮚ in a background of lobular inflammation. The lobule looks disorganized at relatively low power, indicative of the injury to the hepatocytes.



Lobular Inflammation
H&E demonstrates mild hepatocyte swelling →, Kupffer cell hyperplasia ⇨, and lobular inflammation in a case of acute viral hepatitis.



Hepatocyte Swelling
H&E demonstrates lobular disarray characterized by hepatocyte swelling, Kupffer cell hyperplasia, and lobular inflammation in a case of acute viral hepatitis.



Lobular Disarray
H&E shows the diffuse hepatocyte swelling and lobular inflammation atypical of acute viral hepatitis. The lobular injury is typically much more prominent than portal inflammation in acute viral hepatitis.

TERMINOLOGY

Definitions

- Hepatocyte necrosis and inflammation resulting from acute viral infection

ETIOLOGY/PATHOGENESIS

Hepatitis A Virus

- Single-stranded RNA virus in Picornaviridae family
  - Usually spreads via oral or fecal-oral transmission
  - Community outbreaks related to contaminated food or water
- Accounts for ~ 1/2 of acute viral hepatitis cases in USA
- At least 4 genotypes described, but only 1 serotype exists
  - Infection with one genotype confers immunity against all genotypes
- Never results in chronic infection

Hepatitis B Virus

- Partially double-stranded DNA virus in Hepadnaviridae family
- Parenteral, perinatal, and sexual transmission
- Up to 40% of acute hepatitis cases in USA attributable to hepatitis B
- ~ 10% of infected patients develop chronic infection

Hepatitis C Virus

- RNA virus of Flaviviridae family
- Parenteral, perinatal, and sexual transmission
- Accounts for ~ 20% of cases of acute hepatitis
- Only 10-15% of infected individuals develop symptomatic acute hepatitis
- If untreated, ~ 85% of infected patients develop chronic infection

Hepatitis D Virus (Delta Agent)

- Defective RNA virus
- Parenteral and sexual transmission
- Requires coinfection with hepatitis B virus or superinfection in patient with chronic hepatitis B virus infection

Hepatitis E Virus

- Single-stranded, nonenveloped RNA virus in Caliciviridae family
  - 4 routes of infection
  - Vertical transmission
  - Parenteral transmission
  - Consumption of raw or undercooked meat of infected animals
  - Contaminated water supply
- Endemic in parts of Asia, Africa, and India

Other Viruses

- CMV
- Epstein-Barr virus

CLINICAL ISSUES

Presentation

- Nonspecific systemic symptoms: Malaise, fatigue, nausea, vomiting, anorexia, low-grade fever, right upper quadrant pain
- Hepatomegaly
- Jaundice
- Rarely, fulminant hepatic failure

Laboratory Tests

- Elevated transaminases at 5-10x normal values
  - Serologic testing
  - ○ Hepatitis A virus
  - – Detection of antihepatitis A virus IgM in patient with hepatitis or elevated serum aminotransferases is diagnostic of acute hepatitis A virus infection

○ Hepatitis B virus

– Hepatitis B surface antigen (HBsAg) positivity

– Markers of virus replication (HBeAg and hepatitis B virus DNA)

– Antihepatitis B core antigen IgM detectable at symptom onset

○ Hepatitis C virus

– Hepatitis C RNA detectable in serum within 2 weeks after exposure

– Antibodies unreliable in diagnosis of acute hepatitis C virus infection as antibody production may be delayed

– Positive hepatitis C serology must be confirmed with RNA testing because false-positives can occur

○ Hepatitis D virus

– Detection of antihepatitis D virus IgM

○ Hepatitis E virus

– Usually diagnosis of exclusion

– Detection of antihepatitis E virus IgM available in some settings

Treatment

- Drugs
  - ○ No specific drug therapy available for acute hepatitis A virus infection or acute hepatitis E virus infection
  - – Supportive care is mainstay of treatment

○ Antiviral therapy (lamivudine) or immune modulators (interferon) may be

beneficial to select patients with acute hepatitis B

- Direct acting antiviral agents may be used in in acute hepatitis C virus infection

– No advantage to treating acute infection in the postinterferon era, as 20-50% of patients with acute hepatitis C spontaneously clear virus and newer agents highly effective in chronic disease

- Hospitalization recommended for severe or persistent nausea and for patients with signs of developing liver failure
- Liver transplantation considered for patients with acute liver failure

Prognosis

- Most patients with acute hepatitis A virus infection fully recover within 2 months of disease onset
  - 85% of patients with acute hepatitis A virus infection improve with supportive care
  - Fulminant hepatic failure with coagulopathy and encephalopathy is rare
  - Disease severity related to patient age
    – Increased mortality in patients > 40 years of age
    – Patients with preexisting chronic liver disease at increased risk of complications and death

- Atypical variants are well recognized

– Relapsing variant in 3-20% of patients in whom recovery is followed by relapse at 4-15 weeks after initial episode

– ~ 10% develop prolonged cholestasis lasting > 2 weeks

– Possible extrahepatic manifestations include leukocytoclastic vasculitis, arthritis, and glomerulonephritis

- Infection confers lifelong immunity

- ~ 90% of patients with acute hepatitis B virus infection recover fully
  - 1% of acutely infected patients develop fulminant hepatic failure
- Acute hepatitis C may last 2-12 weeks
  - Almost never fulminant
  - Disease is self-limiting in 15% of patients infected with hepatitis C
- Acute hepatitis E follows 2- to 10-week incubation period
  - Illness usually lasts 1-4 weeks
  - Pregnant women and infants at increased risk of mortality

MACROSCOPIC

General Features

- In severe cases with massive necrosis, liver is shrunken, and capsule is flaccid
- Islands of regenerating hepatocytes may form grossly visible nodules that cause concern for malignancy

MICROSCOPIC

Histologic Features

- Lobular disarray
  - Diffuse, mixed lobular inflammatory cell infiltrates
    – Predominantly mononuclear inflammatory cell infiltrates
  - Hepatocyte necrosis
    – Foci of parenchymal collapse evident on trichrome or reticulin stains
  - Hepatocyte swelling
  - Hepatocyte regeneration
  - Kupffer cell hyperplasia
- May see mild portal and periportal inflammation, particularly in acute hepatitis A virus infection
  - Portal inflammation usually less prominent than lobular inflammation and injury
- Pigment-laden macrophages (highlighted on periodic acid-Schiff stain)
- Areas of confluent hepatocyte necrosis in severe cases
- Canalicular cholestasis present in some cases
- Fibrosis characteristically absent unless there is preexisting chronic liver disease
- Usually recognized clinically, so liver biopsy seldom performed

DIFFERENTIAL DIAGNOSIS

Autoimmune Hepatitis

- Although by definition chronic disease, initial clinical presentation may reflect acute or fulminant hepatitis
- Characterized clinically by positive autoimmune serologies (ANA, anti-SMA, anti-LKM)
- Polyclonal hypergammaglobulinemia often seen
- Portal and periportal hepatitis often present in addition to lobular hepatitis, often with prominent plasma cells
- Fibrosis often present at presentation
- Most cases highly responsive to immunosuppressive therapy
- Acute viral serologies negative

Drug- or Toxin-Induced Hepatitis

- Usually cannot be reliably distinguished from acute viral hepatitis based on histology
- Eosinophils may be prominent but are not sensitive or specific feature
- Generally self-limited and resolves after withdrawal of drug
- Diagnosis requires clinical history of exposure
- Acute viral serologies negative

Wilson Disease

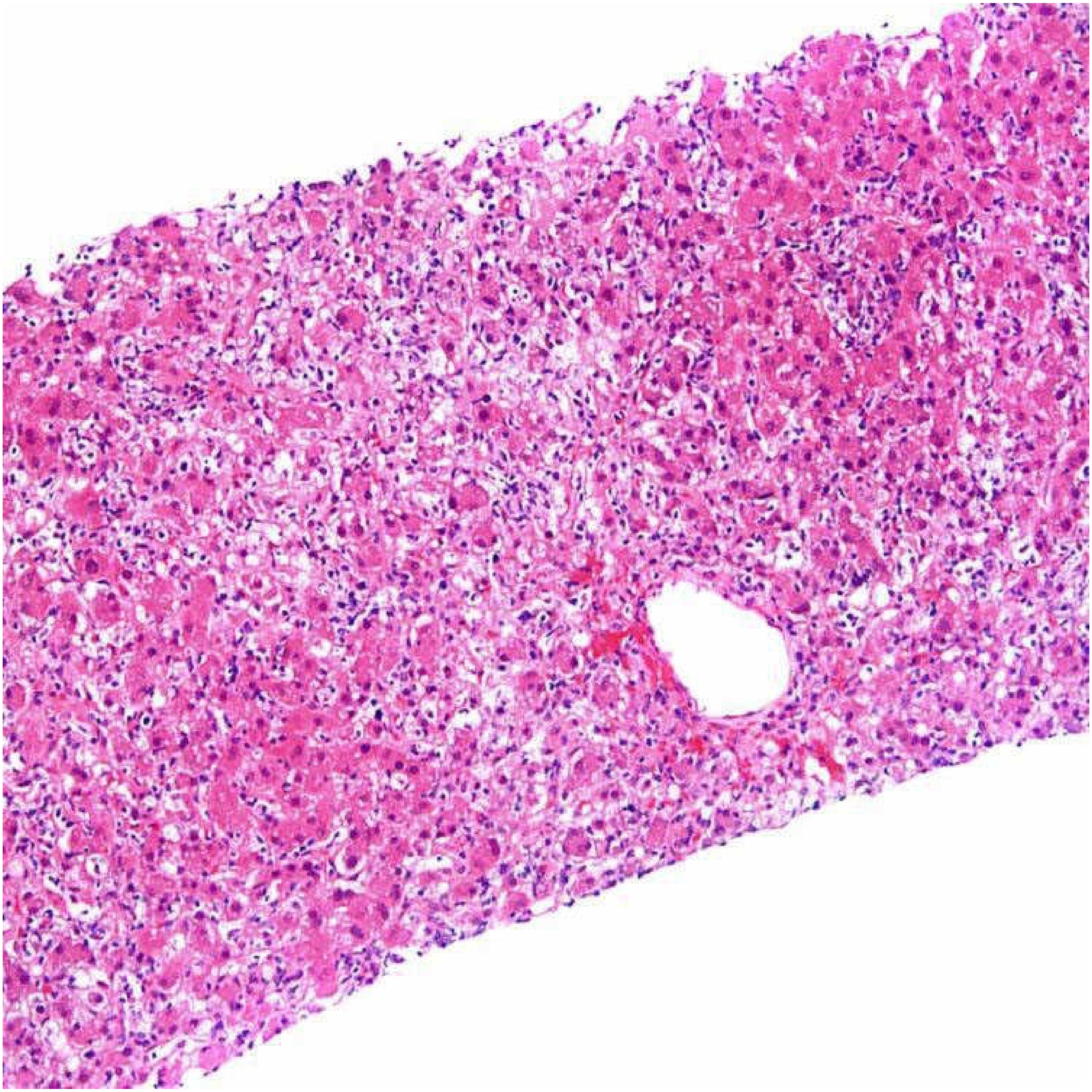
- Rarely presents as fulminant hepatitis
- Quantitative copper testing shows elevated liver copper level
- Acute viral serologies negative

Ischemia

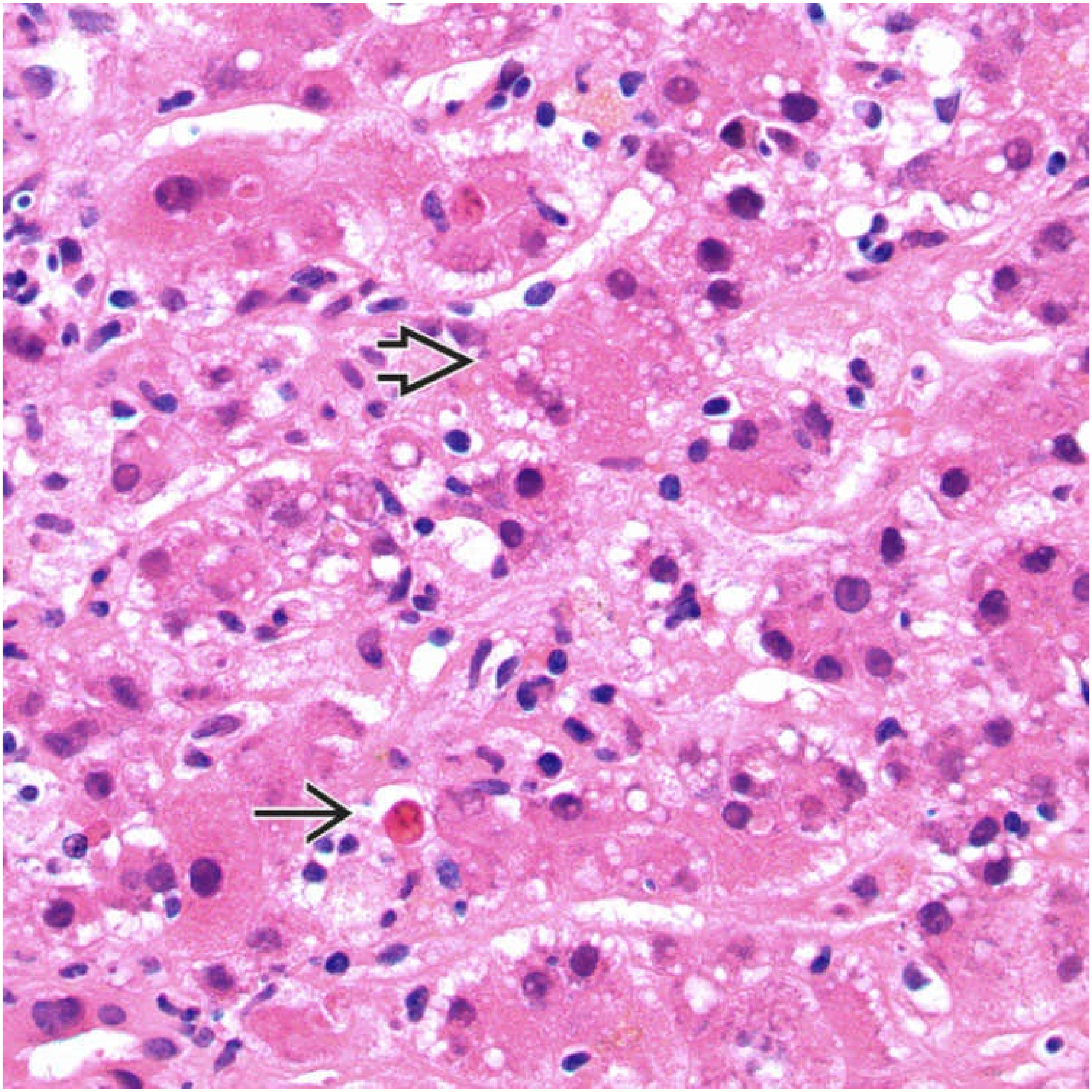
- Characterized clinically by sharp and marked rise in serum aminotransferases
    - Aminotransferases also decline quickly with recovery
- Focal or diffuse centrilobular hepatocyte necrosis
- Lobular inflammation and hepatocyte swelling are not major features
- Often associated with vascular injury or hypercoagulable state
- Acute viral serologies negative

Idiopathic Hepatitis or Hepatic Failure

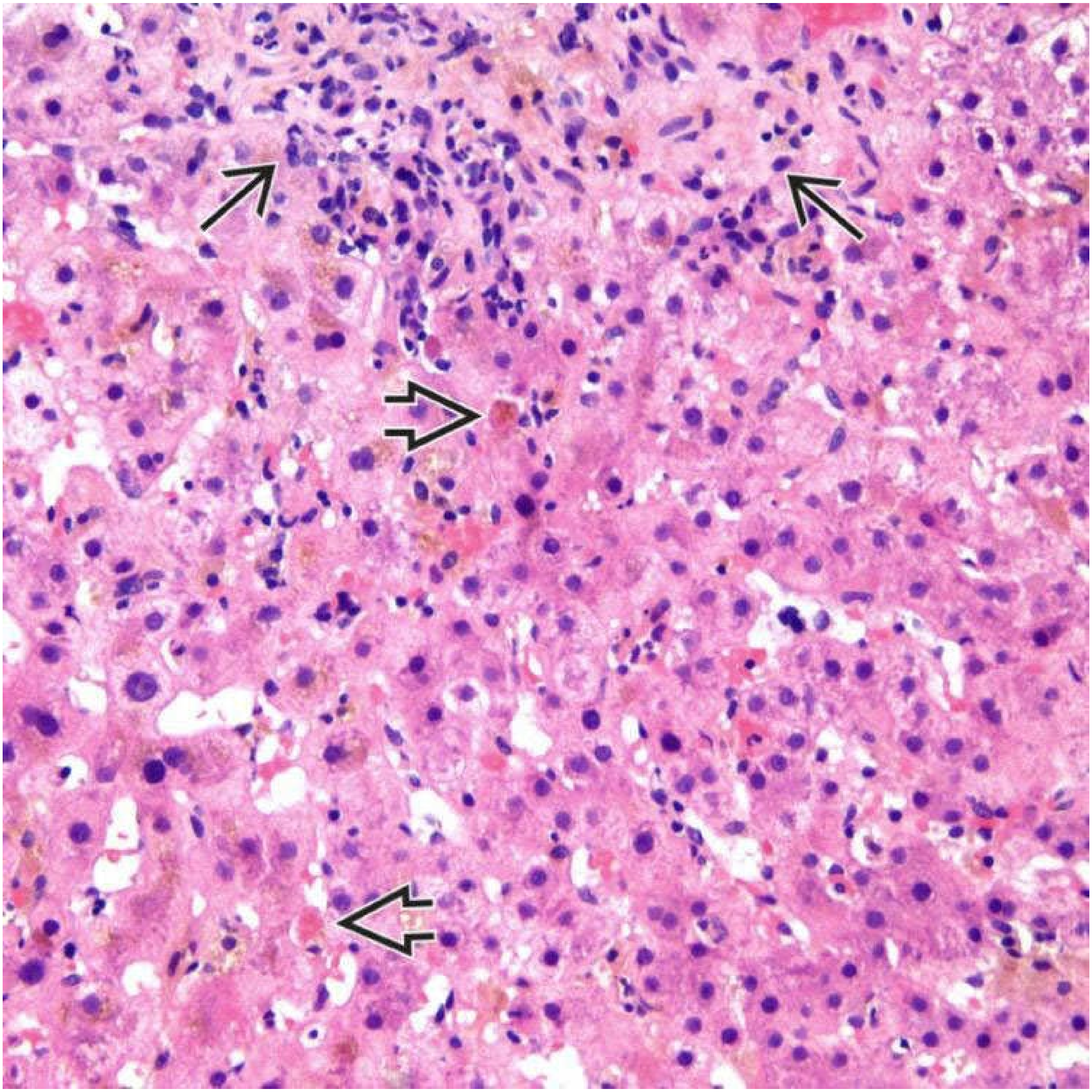
- Subset of cases in which etiology cannot be determined



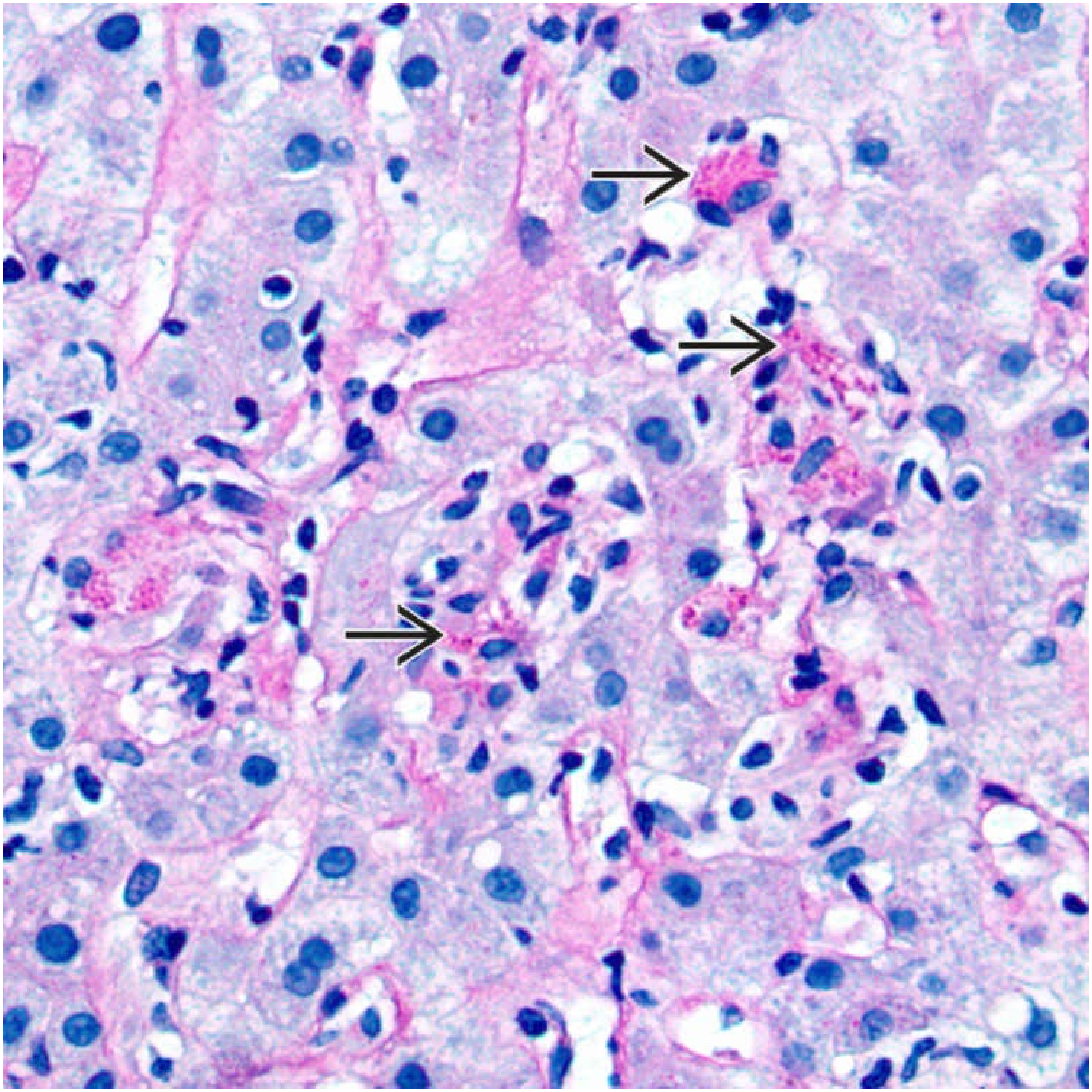
Lobular Hepatitis
Low-power view of a liver biopsy with acute hepatitis B shows lobular disarray characterized by marked hepatocyte swelling and injury. There is also brisk lobular inflammation.



Hepatocyte Injury
This biopsy shows hepatocyte swelling ⇨ and single cell necrosis → associated with mild lobular inflammation.

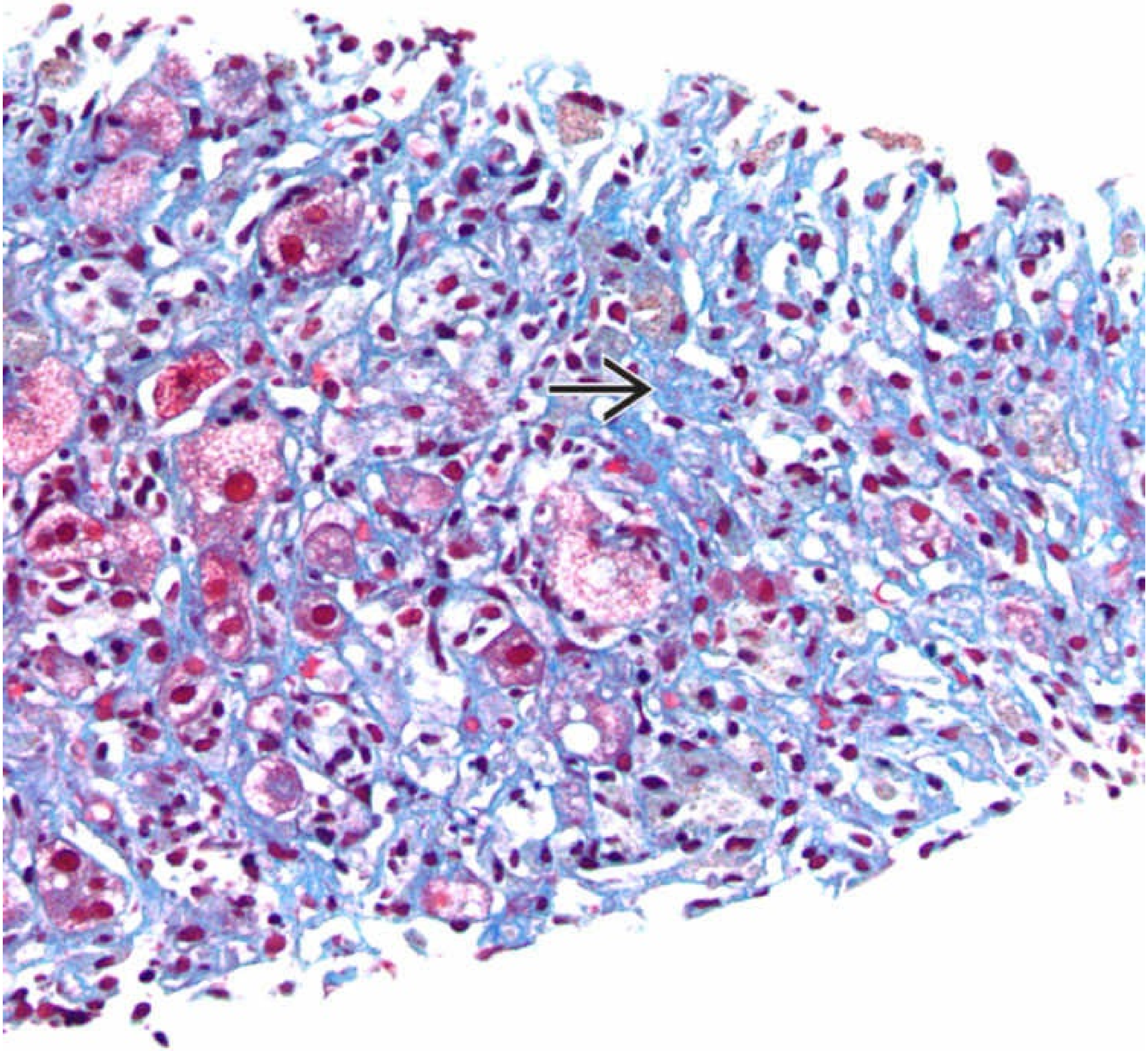


Cholestasis
This case of acute hepatitis B shows cholestasis as well as lobular disarray and numerous necrotic hepatocytes ⇨. Mild periportal inflammation and ductular reaction are also seen →, but the portal findings are less prominent than the lobular injury.

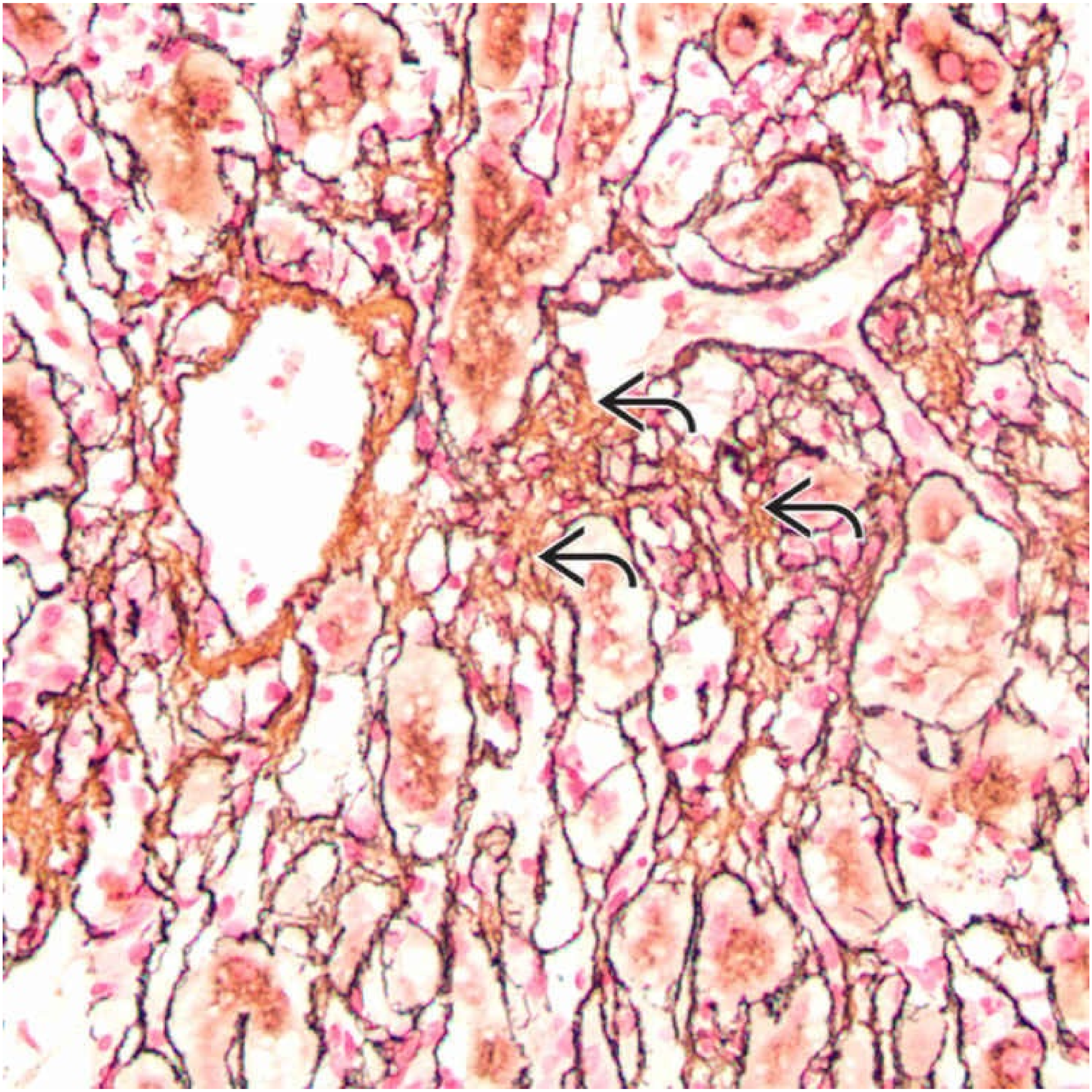


Kupffer Cell Hyperplasia

Periodic acid-Schiff with diastase digestion shows increased numbers of pigmented Kupffer cells with granular staining → highlighted.



Parenchymal Collapse
Masson Trichrome demonstrates only pale gray-blue staining → in areas of hepatocyte necrosis and parenchymal collapse. This is a case of fulminant liver injury due to acute viral hepatitis.



Reticulin Collapse
Reticulin stain highlights areas of collapse of the reticulin framework secondary to hepatocyte necrosis and parenchymal loss.

SELECTED REFERENCES

1. Price, J. An update on hepatitis B, D, and E viruses. *Top Antivir Med*. 2014; 21(5):157–163.
2. Ramachandran, S, et al. Recent population expansions of hepatitis B virus in the United States. *J Virol*. 2014; 88(24):13971–13980.
3. Liang, TJ. Hepatitis B: the virus and disease. *Hepatology*. 2009; 49(5 Suppl):S13–S21.
4. Fabris, P, et al. Acute hepatitis C: clinical aspects, diagnosis, and outcome of acute HCV infection. *Curr Pharm Des*. 2008; 14(17):1661–1665.
5. Ichai, P, et al. Etiology and prognosis of fulminant hepatitis in adults. *Liver Transpl*. 2008;

14(Suppl 2):S67–S79.
6. Kamal, SM. Acute hepatitis C: a systematic review. *Am J Gastroenterol*. 2008; 103(5):1283–1297. [quiz 1298].
7. Turner, J, et al. Hepatitis e: a UK perspective. *Br J Hosp Med (Lond)*. 2008; 69(9):517–519.
8. Cuthbert, JA. Hepatitis A: old and new. *Clin Microbiol Rev*. 2001; 14(1):38–58.
9. Krawczynski, K, et al. Hepatitis E: an overview. *Minerva Gastroenterol Dietol*. 1999; 45(2):119–130. [discussion 130-5].
10. Kobayashi, K, et al. Liver biopsy features of acute hepatitis C compared with hepatitis A, B, and non-A, non-B, non-C. *Liver*. 1993; 13(2):69–72.
11. Sciot, R, et al. Cholestatic features in hepatitis A. *J Hepatol*. 1986; 3(2):172–181.

Hepatitis B

KEY FACTS

Etiology/Pathogenesis

- Partially double-stranded DNA virus
  - Typically transmitted vertically, parenterally, or sexually

Clinical Issues

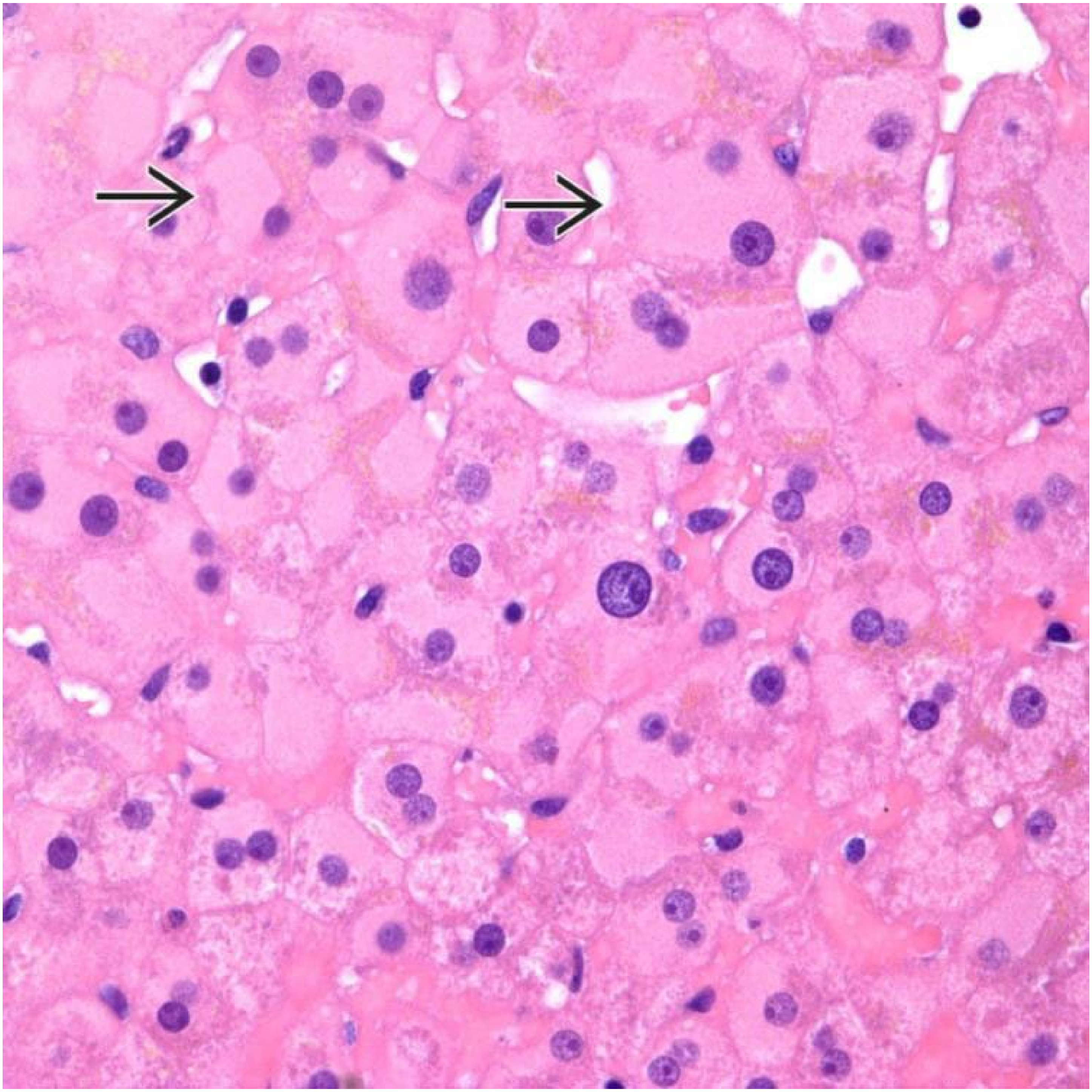
- 10% of infected patients become chronically infected
  - 400 million people worldwide have chronic HBV
- Symptoms include mild flu-like syndrome, nausea, vomiting, jaundice
  - > 50% are asymptomatic
- Lifelong risk of developing cirrhosis &/or HCC
- Useful laboratory tests include serology for HBV viral antigens, anti-HBV antibodies, and HBV DNA viral load

Microscopic

- Acute hepatitis B
  - Hepatocytic swelling, predominantly lobular inflammation, spotty necrosis
  - Severe cases may show confluent and bridging necrosis, collapse of hepatocytic cords, hepatocytic regeneration
- Chronic hepatitis B
  - Portal-based inflammation with variably present ground-glass hepatocytes, "sanded nuclei" in hepatocytes, variable fibrosis
    - Stage of fibrosis indicates disease progression and is important therapeutic and prognostic indicator
- Immunohistochemistry for HBcAG and HBsAG may be useful, but not invariably positive

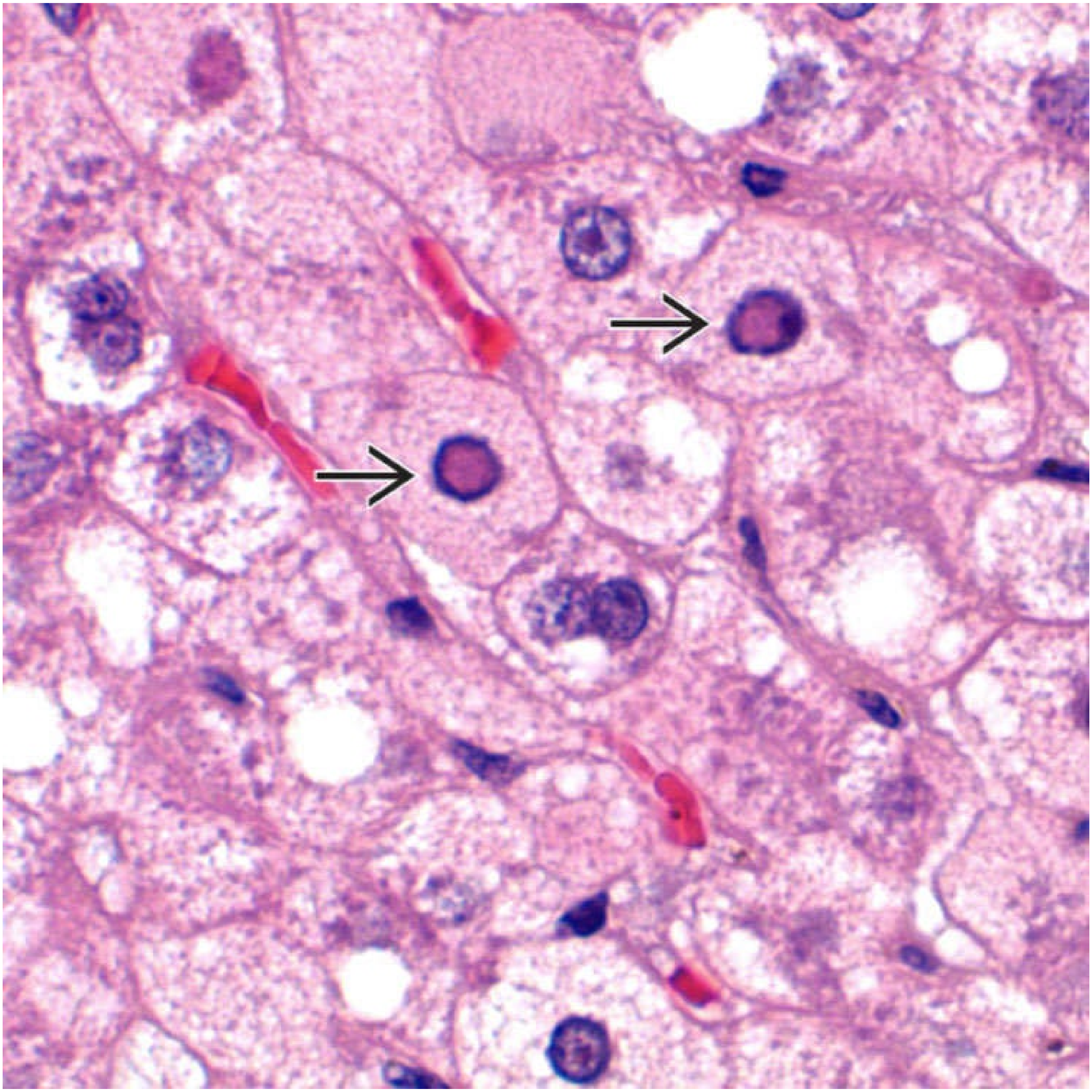
Top Differential Diagnoses

- Hepatitis A, hepatitis C, autoimmune hepatitis, other viral infections (CMV, EBV)
  - Histologic features may be very nonspecific, so correlation with history and serology is crucial

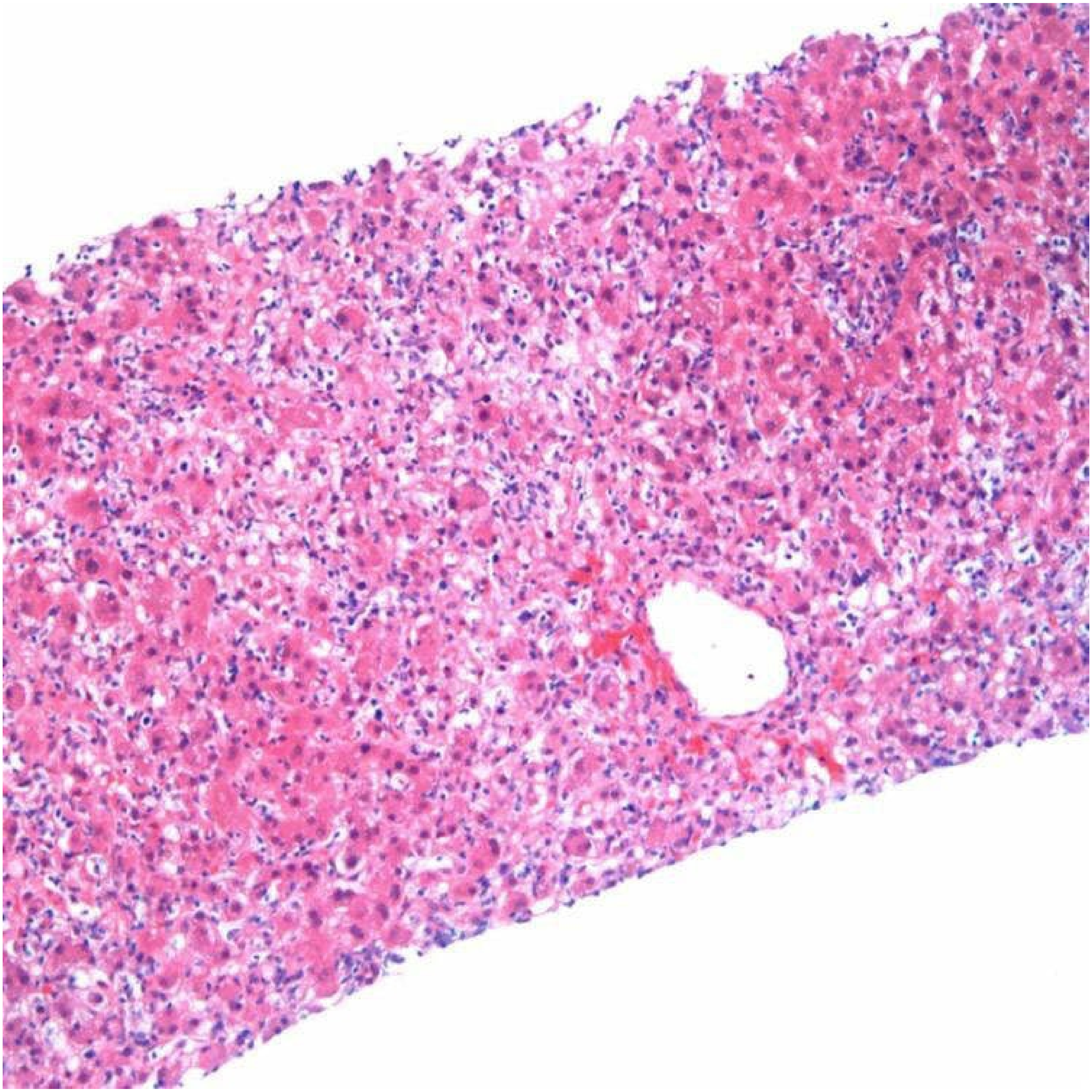


Ground-Glass Hepatocytes

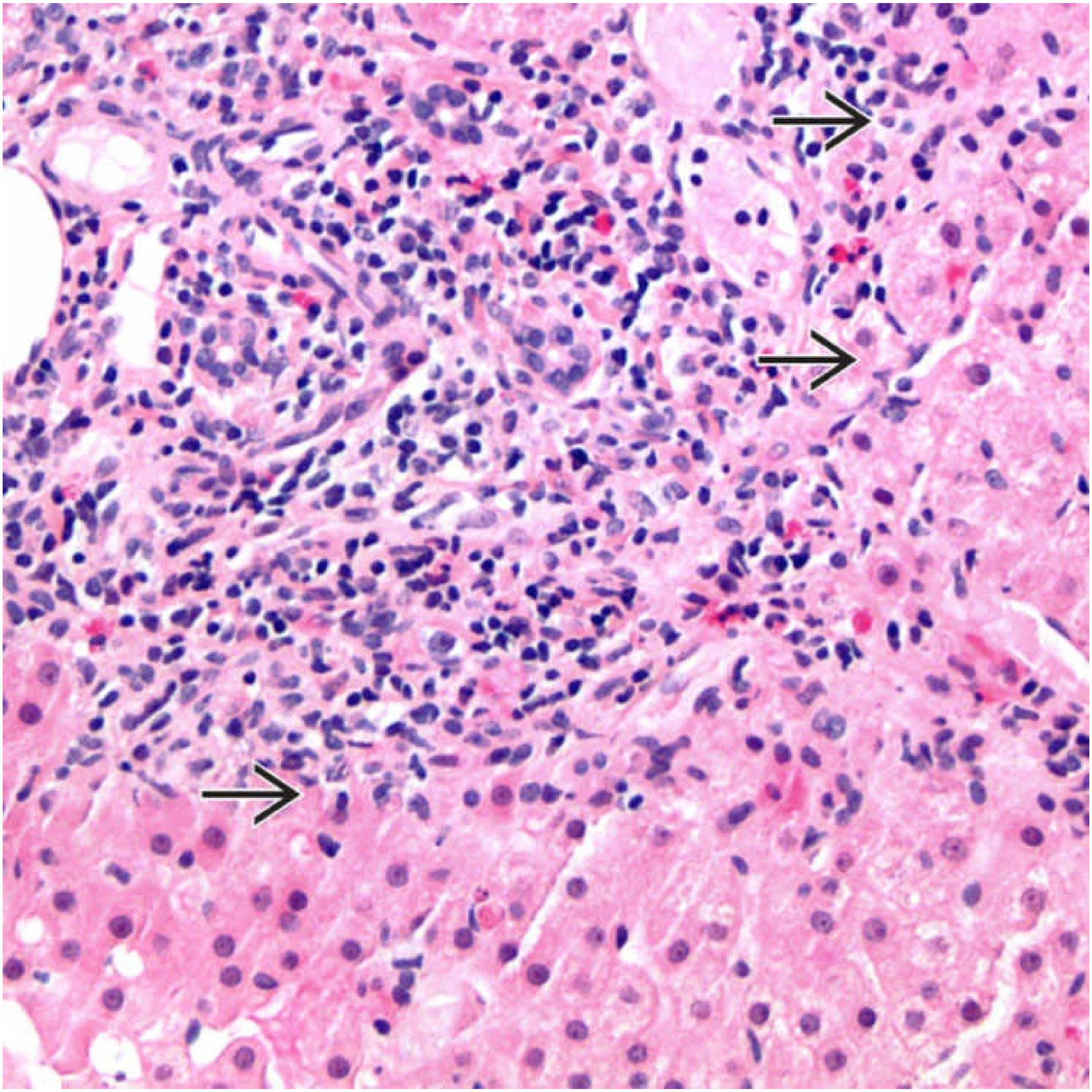
Ground-glass hepatocytes → have glassy eosinophilic cytoplasm representing proliferation of smooth ER in response to HBsAg.



Sanded Nuclei
Hepatitis B-infected hepatocytes may have pale pink, finely granular intranuclear inclusions (sanded nuclei →) representing nuclear accumulation of HBcAg. These may be hard to detect on routine H&E staining.



HBV, Acute
This case of acute HBV infection shows lobular disarray with marked hepatocyte swelling and lobular inflammation.



HBV, Chronic
This section shows interface hepatitis in chronic hepatitis B consisting of chronic inflammatory cells that extend beyond the limiting plate → into the periportal parenchyma.

TERMINOLOGY

Abbreviations

- Hepatitis B virus (HBV)

Synonyms

- Australia antigen: Hepatitis B surface antigen (HBsAg)

Definitions

- Infection by HBV
  - Member of Hepadnaviridae family
  - Genome comprises partially double-stranded DNA virus

ETIOLOGY/PATHOGENESIS

Infectious Agents

- Transmitted parenterally
  - Vertical transmission: Mothers to newborn infants
  - Horizontal transmission: Between young children
  - Sexual contact
- Liver injury appears to be immune mediated
  - HBV-specific T cells play key role in pathogenesis and viral clearance

CLINICAL ISSUES

Epidemiology

- Incidence
  - 400 million people worldwide are chronically infected with HBV

Presentation

- Acute hepatitis B
  - Symptoms include mild flu-like symptoms, nausea, vomiting, jaundice
    - > 50% are asymptomatic
  - < 1% develop fulminant liver failure leading to death or liver transplantation
  - Serum HBsAg and anti-HBc virus IgM Ab positive
- Chronic hepatitis B
  - Serum HBsAg positive and anti-HBc virus IgM Ab negative

Laboratory Tests

- Serology for HBV viral antigens: HBsAg, HBcAg, HBeAg
- Serology for anti-HBV antibodies: Anti-HBs, anti-HBc, anti-HBe
- Serum HBV DNA and viral load
- Elevated transaminases

Natural History

- 10% of infected individuals become chronically infected
  - Life-long risk of developing cirrhosis &/or HCC in chronic hepatitis B
  - ○ Cirrhosis is not prerequisite for developing HCC
  - – HBV viral genome can act as oncoprotein and intergrade into host genome
- Coinfection with HIV, HCV, and hepatitis D virus (HDV) is common, as they share common transmission route

Treatment

- Drugs
  - ○ Nucleoside analogue therapy: Lamivudine, adefovir, entecavir
  - ○ Interferon

MACROSCOPIC

Cirrhosis

- Nodularity (macronodular or mixed macro- and micronodular) and scarring

MICROSCOPIC

Histologic Features

- Acute hepatitis B
  - ○ Hepatocytic swelling, lobular disarray, and predominantly lobular inflammation
  - – Mainly mononuclear, including lymphocytes, plasma cells, and Kupffer cells

○ Apoptotic hepatocytes and spotty necrosis

○ Some cases may show marked cholestasis

○ Confluent and bridging necrosis in severe cases with parenchymal collapse and hepatocyte regeneration

– Collapse best demonstrated by reticulin stain

○ Immunohistochemistry generally not useful in acute HBV, as virus is rapidly eliminated and thus not detectable

- Chronic hepatitis B
  - ○ Portal-based inflammation
    - – Mononuclear inflammatory cells infiltrates, composed predominantly of lymphocytes admixed with Kupffer cells and plasma cells
    - – May expand portal tracts
  - ○ Interface hepatitis (previously termed piecemeal necrosis)
    - – Mononuclear inflammatory cells and apoptotic hepatocytes beyond limiting plate
  - ○ Lobular hepatitis
    - – Aggregates of mononuclear inflammatory cells, apoptotic hepatocytes, hepatocytic debris, &/or

confluent necrosis
  - Fibrosis
    - Begins in portal regions, extends beyond limiting plate, then forms bridging septa between portal-portal and portal-central regions and ultimately cirrhosis
  - Ground-glass hepatocytes
    - Finely granular cytoplasmic inclusion
    - Pushes cellular contents and nucleus to side due to proliferation of smooth ER in response to abundant HBsAg
    - Can be highlighted by Shikata Orcein stain, Victoria Blue stain, and anti-HBs immunohistochemical stain
    - Indicates chronic hepatitis B infection
    - Not specific for hepatitis B
  - Sanded nuclei of hepatocytes
    - Pale pink granular inclusions in hepatocytic nuclei containing HBcAg
    - Can be highlighted by anti-HBc immunohistochemical stain
    - Extensive nuclear staining for anti-HBc indicates active HBV viral replication and may suggest immunosuppression status
- Fibrosing cholestatic hepatitis B
  - Variant of viral hepatitis B that often has more progressive course and worse outcome
  - Pathogenesis is thought to be due to viral cytopathic effect
  - Typically occurs following orthotopic liver transplantation, but also occurs in other immunosuppressed states
    - Occurrence is currently less common due to better prevention and antiviral regimens
  - Unique histopathology
    - Hepatocytic swelling due to cholestasis
    - Canalicular and bile ductal cholestasis
    - Marked bile ductular reaction
    - Extensive fibrosis extending from portal tracts, surrounding hepatocytes within sinusoidal spaces, with serpiginous pattern
- Immunohistochemistry for HBcAg and HBsAg may be useful, but not invariably positive

Semiquantitative Grading and Staging

- Grading denotes inflammatory activity while staging indicates degree of fibrosis
- Stage of fibrosis indicates disease progression and is important therapeutic and prognostic indicator
- Ishak score or Batts/Ludwig system most commonly used

DIFFERENTIAL DIAGNOSIS

Hepatitis A

- Positive hepatitis A serology (anti-HAV IgM)
- Negative HBV serology
- Often history of travel or food poisoning

Autoimmune Hepatitis

- Positive autoimmune serology (ANA, anti-SMA, LKM, SLA)
- Negative HBV serology (HBsAg, anti-core IgM, anti-core IgG)
- More prominent plasma cells
- Responds to steroids

Chronic Hepatitis C

- Positive anti-HCV antibody and HCV RNA in serum
- Negative HBV serology
- Portal lymphoid aggregates, Poulsen (bile duct) lesion, and steatosis more common in hepatitis C

Drug-Associated Hepatitis

- Medication history that corresponds to onset of liver disease
  - Symptoms ideally resolve after drug withdrawal
- Negative HBV serologies
- Eosinophils may be prominent

Hepatitis E

- Positive travel history and anti-HEV serology

Other Viral Hepatitides

- CMV hepatitis
  - Neutrophilic microabscesses typical
  - Characteristic viral inclusions
- EBV hepatitis
  - Atypical lymphocytes in lobules, especially those lining sinusoidal space in bead-like appearance
- Herpes simplex virus hepatitis
  - Confluent necrosis mimicking ischemia
  - Typical syncytial cell virus inclusion
- Yellow fever
  - Positive travel history and virologic studies
- Dengue fever
  - Positive travel history and virologic studies
- Syphilitic hepatitis
  - Positive serology
  - Warthin-Starry stain or immunostain for *Treponema pallidum*

Primary Biliary Cholangitis

- Elevated antimitochondrial antibody, alkaline phosphatase, GGT
- Alkaline phosphatase typically elevated out of proportion to transaminases

- Predominantly affecting middle-aged women
- Duct destruction not characteristic of HBV infection

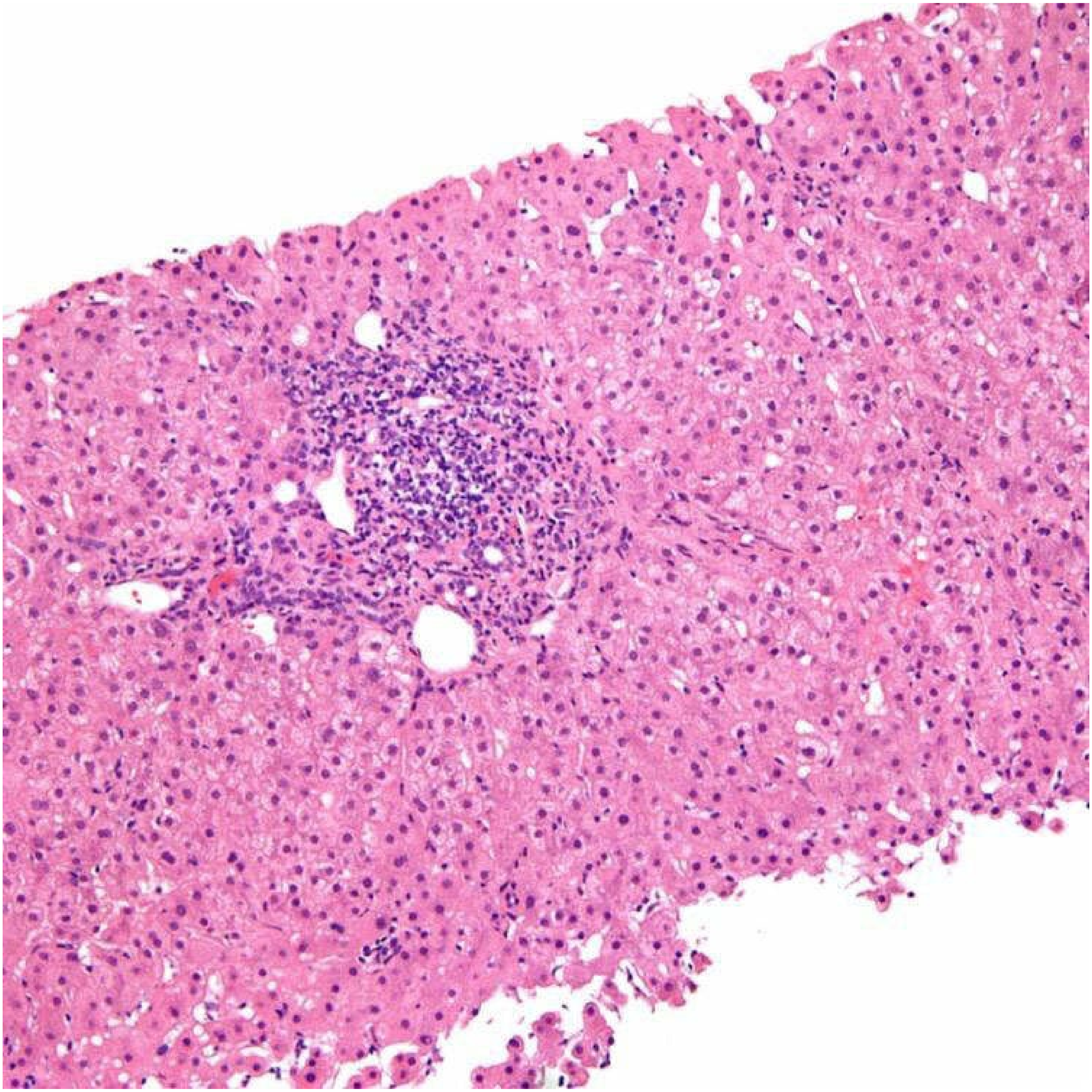
Other Causes of Ground-Glass Cells

- Lafora disease
  - Cyanamide toxicity
  - Fibrinogen storage disease
  - Glycogen pseudo-ground-glass cell change
    - Commonly seen in immunosuppressed individuals and post liver transplant

DIAGNOSTIC CHECKLIST

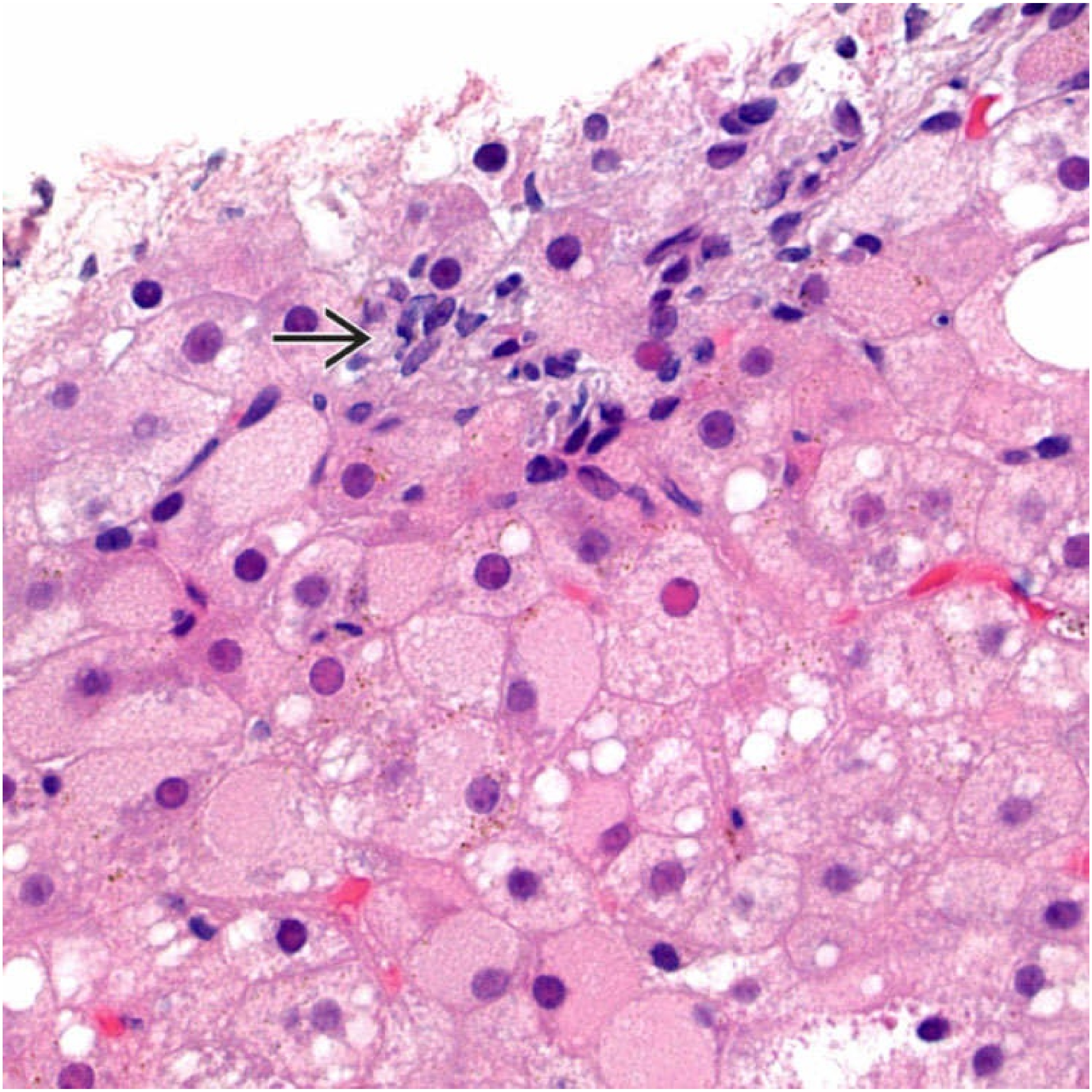
Pathologic Interpretation Pearls

- Purpose of liver biopsy is to grade and stage HBV-induced liver disease and exclude concomitant liver diseases
  - HBV coinfection with other viruses, such as HCV, HDV, and HIV, is common
    - Correlation with clinical history and serology is important
- Unlike hepatitis C, recurrent hepatitis B after liver transplantation is rare due to advent of antiviral prophylaxis
  - Be cautious not to overdiagnose recurrent hepatitis B in posttransplant biopsy



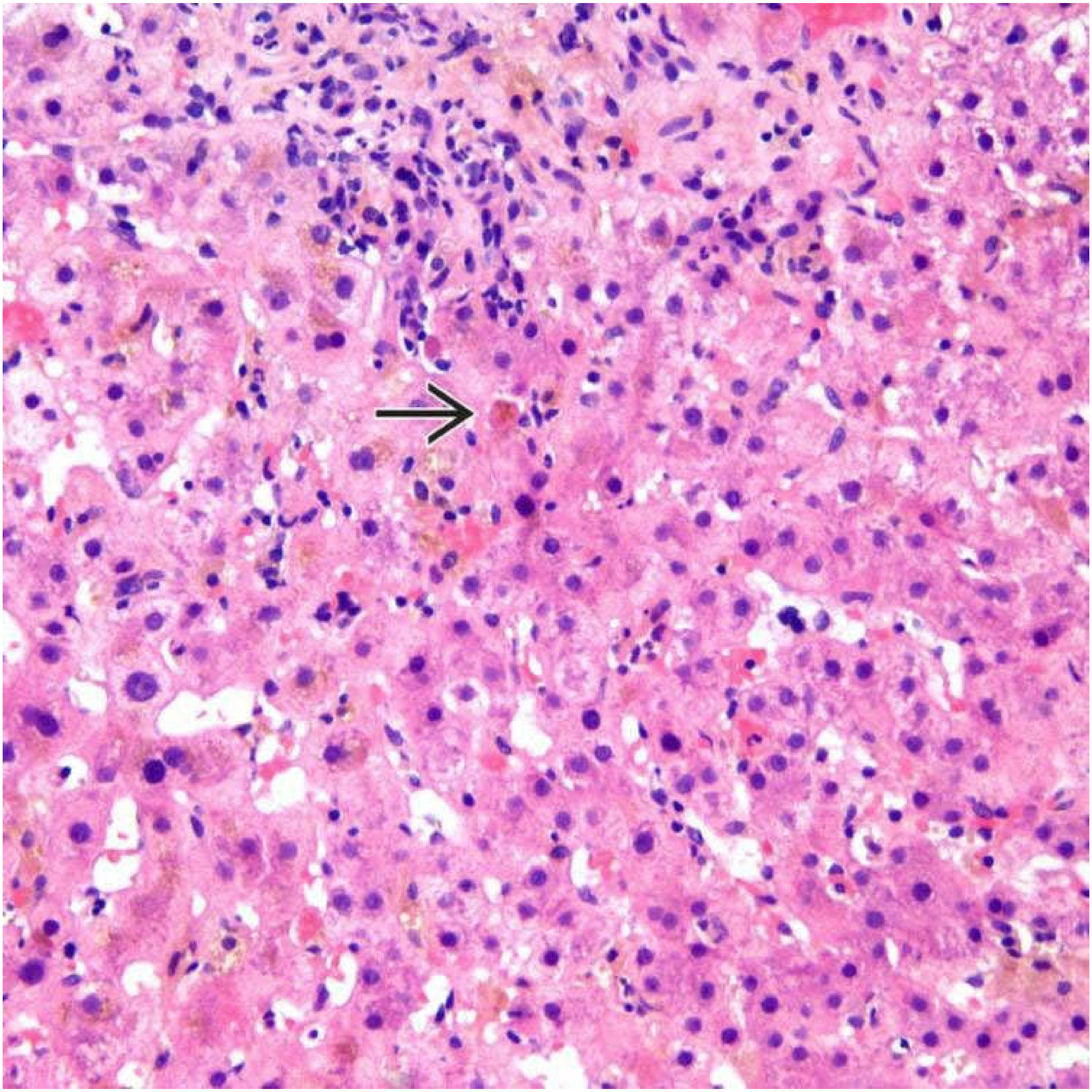
HBV, Chronic

The features of chronic hepatitis B are often nonspecific, as seen in this biopsy with portal-based mononuclear cell inflammation. HBV and HCV can appear quite similar histologically and may also coexist.



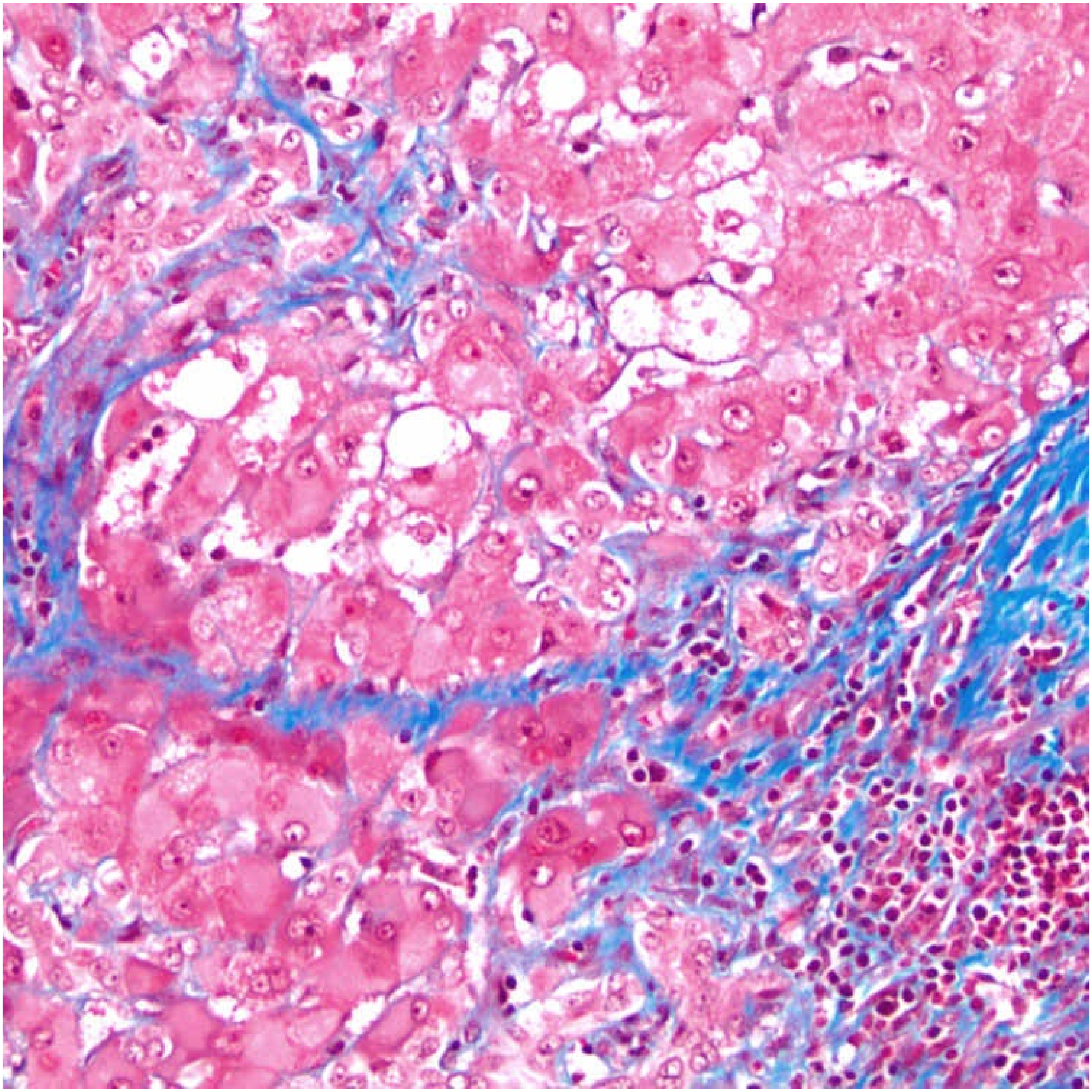
Lobular Inflammation

H&E section demonstrates a focus of lobular inflammation composed of lymphocytes and Kupffer cells →. Ground-glass cells and sanded nuclei are present in surrounding hepatocytes.



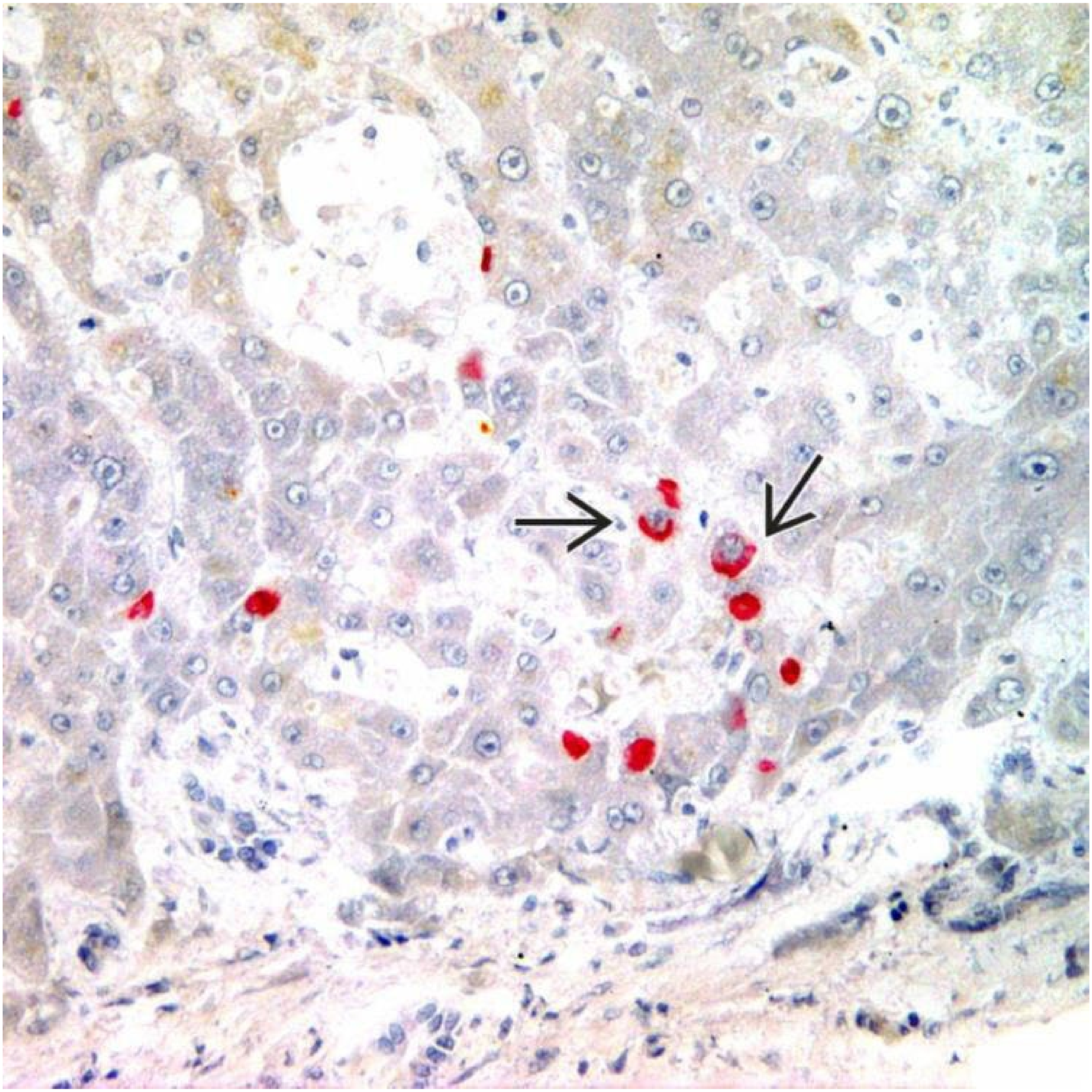
HBV, Acute

This case of acute hepatitis B shows lobular inflammation and scattered apoptotic hepatocytes →. This case also has cholestatic features, which are occasionally seen in acute HBV infection.

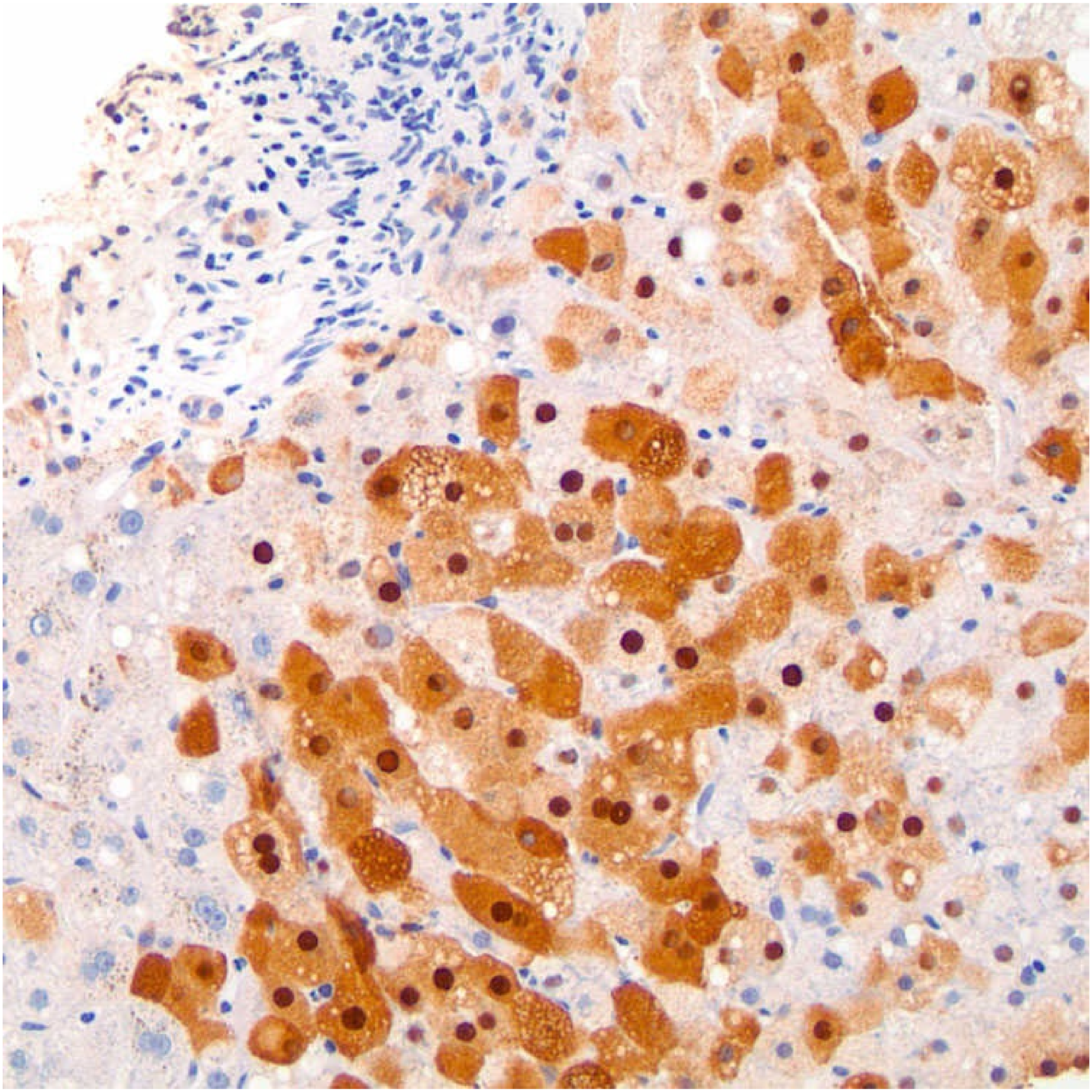


Fibrosis

Masson trichrome stain shows collagen strands that extend beyond portal tracts to reach the central region and form bridging septa in chronic hepatitis B.



Immunohistochemistry for Surface Antigen
Positive cytoplasmic staining for hepatitis B surface antigen often forms a perinuclear crescent → .



Immunohistochemistry for Core Antigen
Immunohistochemical stain for anti-HBc (core antigen) shows both cytoplasmic and nuclear staining.

SELECTED REFERENCES

1. Halegoua-De Marzio, D, et al. Then and now: the progress in hepatitis B treatment over the past 20 years. *World J Gastroenterol*. 2014; 20(2):401–413.
2. Trépo, C, et al. Hepatitis B virus infection. *Lancet*. 2014; 384(9959):2053–2063.
3. Whittaker, G, et al. Hepatitis B in pregnancy. *South Med J*. 2014; 107(3):195–200.
4. Pol, S. Management of HBV in immunocompromised patients. *Liver Int*. 2013; 33(Suppl 1):182–187.
5. Liang, TJ. Hepatitis B: the virus and disease. *Hepatology*. 2009; 49(5 Suppl):S13–S21.
6. Mani, H, et al. Liver biopsy findings in chronic hepatitis B. *Hepatology*. 2009; 49(5 Suppl):S61–

S71.
7. McMahon, BJ. The natural history of chronic hepatitis B virus infection. *Hepatology*. 2009; 49(5 Suppl):S45–S55.
8. Goodman, ZD. Grading and staging systems for inflammation and fibrosis in chronic liver diseases. *J Hepatol*. 2007; 47(4):598–607.
9. Harrison, TJ. Hepatitis B virus: molecular virology and common mutants. *Semin Liver Dis*. 2006 May; 26(2):87–96. [Review. Erratum in: Semin Liver Dis. 26(3): 304-5, 2006].
10. Wisell, J, et al. Glycogen pseudoground glass change in hepatocytes. *Am J Surg Pathol*. 2006; 30(9):1085–1090.
11. Harrison, RF, et al. Recurrent hepatitis B in liver allografts: a distinctive form of rapidly developing cirrhosis. *Histopathology*. 1993; 23(1):21–28.
12. Ishak, KG. Light microscopic morphology of viral hepatitis. *Am J Clin Pathol*. 1976; 65(5 Suppl):787–827.

Hepatitis C

KEY FACTS

Terminology

- Hepatitis, usually chronic, secondary to hepatitis C virus (HCV) infection
  - Worldwide seroprevalence of HCV antibodies (anti-HCV) estimated at 3%
  - Estimated 3-4 million persons infected in United States

Etiology/Pathogenesis

- Common modes of transmission include blood transfusion, needle stick

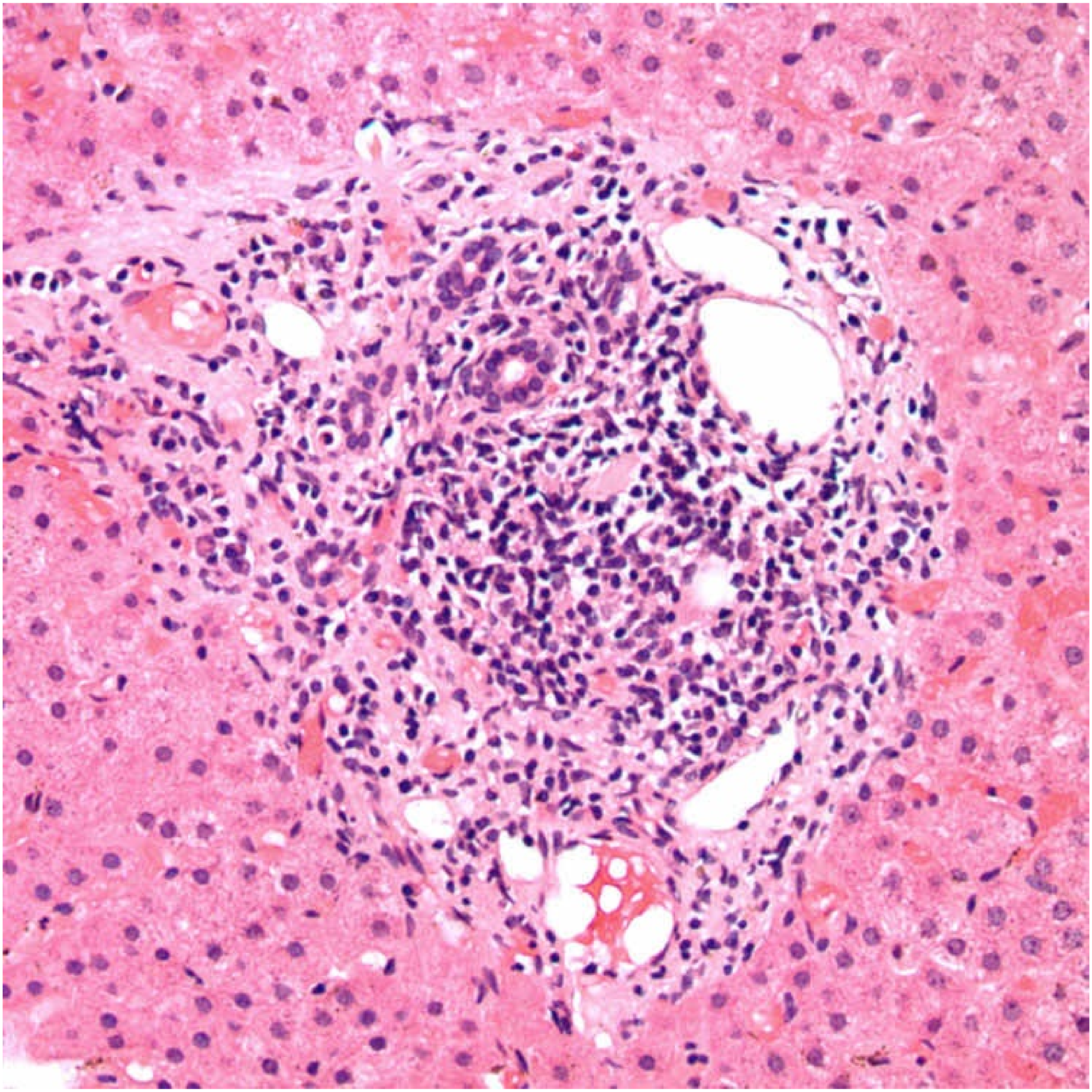
Clinical Issues

- Presenting symptoms nonspecific (fatigue, anorexia, nausea)
  - Many patients asymptomatic
- Liver biopsy to grade and stage disease and exclude other liver diseases
  - Grade indicates degree of necroinflammatory activity
  - Stage indicates extent of fibrosis
    - Stage drives treatment decisions as well
- Usually progressive disease, leading to cirrhosis, liver failure, risk of hepatocellular carcinoma
- Treatment
  - Standard therapy historically is pegylated interferon-α in combination with ribavirin
  - Newer drugs are highly effective with fewer side effects
- Laboratory tests
  - Anti-HCV antibodies
  - HCV RNA by PCR testing

Microscopic

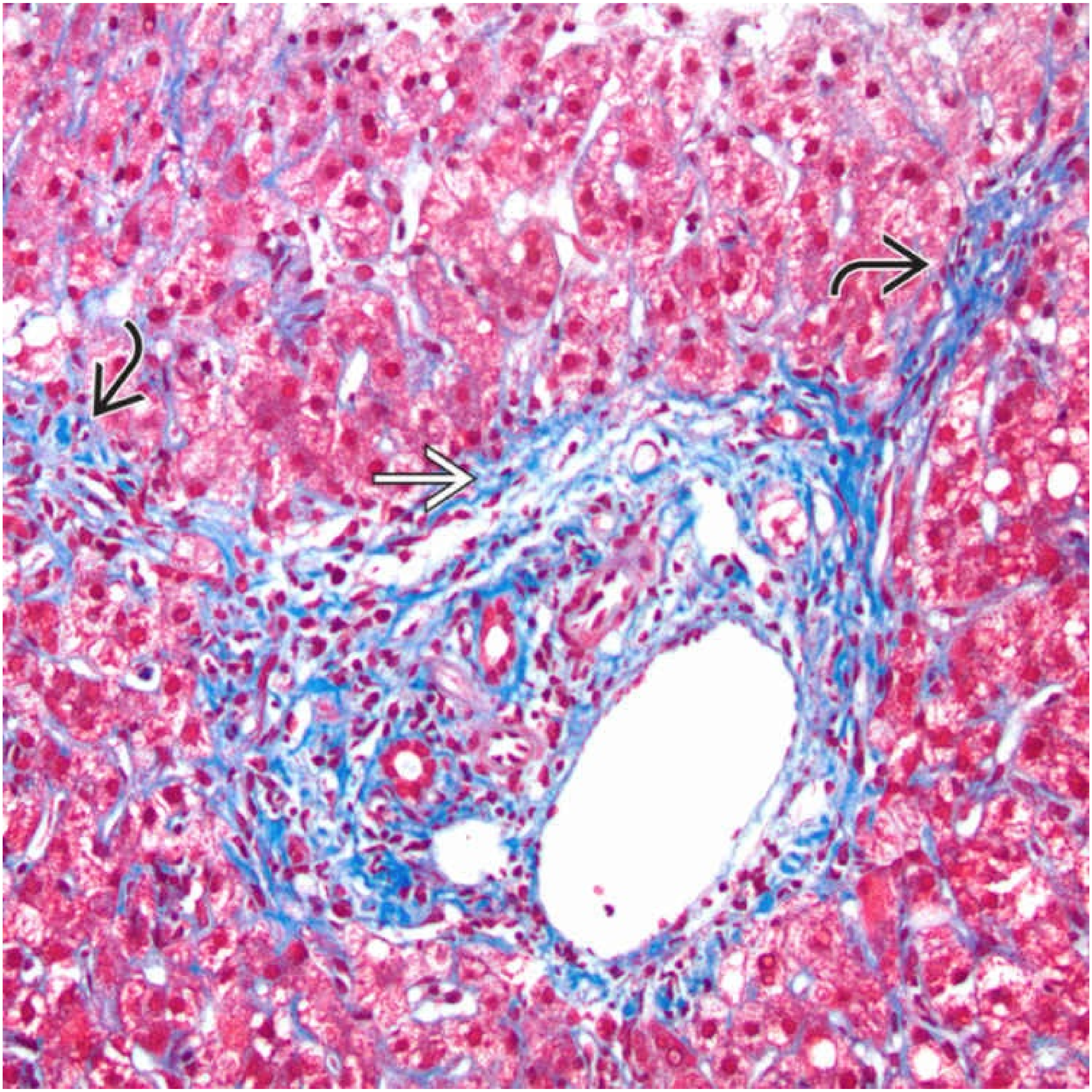
- Variably dense portal lymphocytic infiltrates
  - Periportal interface activity
  - Portal lymphoid aggregates
  - Patchy steatosis

• Scattered lobular collections of inflammatory cells ± acidophil bodies

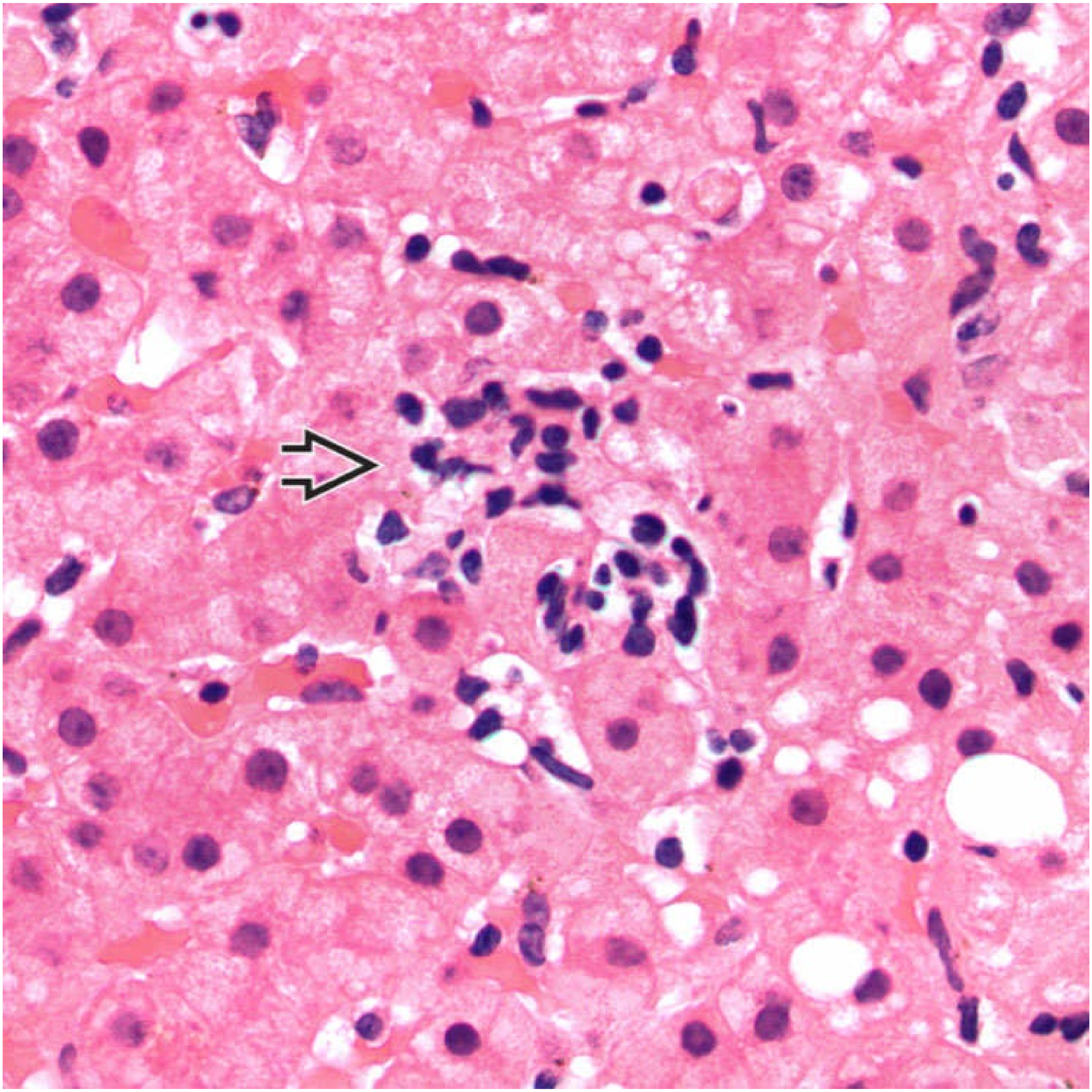


Portal Inflammation

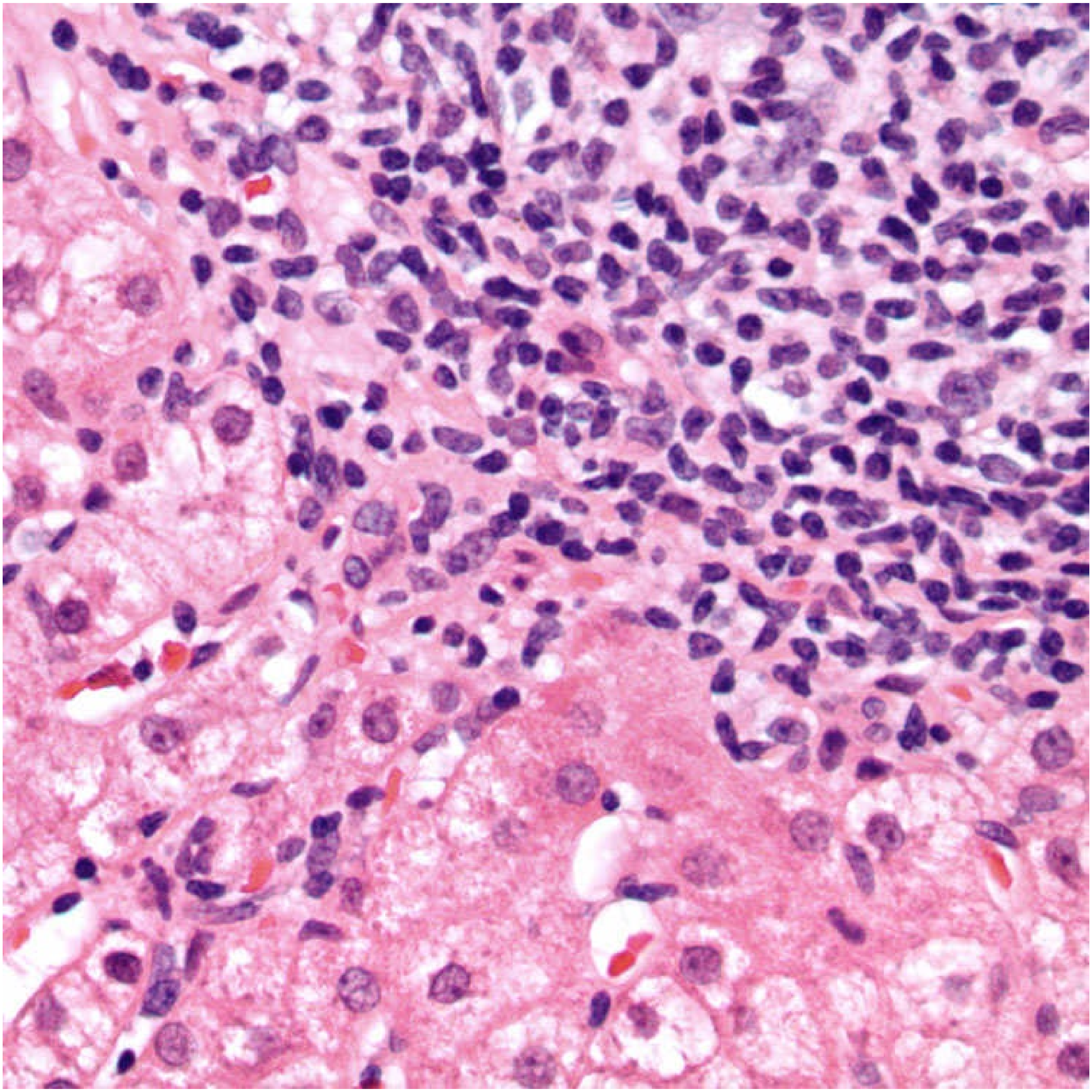
The inflammation in hepatitis C is typically portal-based and composed primarily of lymphocytes.



Portal/Periportal Fibrosis
Trichrome stain demonstrates portal fibrous expansion ⇒ as well as periportal fibrous extension ↷. The periportal fibrous extension makes this biopsy a stage 2.



Lobular Inflammation
A lobular collection of inflammatory cells ⇨ is seen in a case of chronic hepatitis C virus (HCV) infection.



Interface Hepatitis
Lymphocytes extending past the limiting plate and infiltrating surrounding hepatocytes is known as interface activity. Mild hepatocyte swelling, eosinophilia, and necrosis are often evident, reflecting the resultant hepatocyte injury.

TERMINOLOGY

Abbreviations

- Hepatitis C virus (HCV) infection

Definitions

- Hepatitis, usually chronic, secondary to HCV infection

ETIOLOGY/PATHOGENESIS

Infectious Agents

- Enveloped, single-stranded RNA virus of Flaviviridae family
  - Inherent high mutation rate generates viral heterogeneity
  - 6 viral genotypes and > 50 subtypes
  - – Vary in geography, mode of transmission, and response to treatment
- Virus is directly cytopathic and induces immune-mediated cellular injury

Modes of Transmission

- Blood transfusion, needlestick inoculation
- Perinatal exposure, probably occurs with low efficiency
- Efficiency of sexual transmission is controversial but probably low

CLINICAL ISSUES

Epidemiology

- Incidence
  - Worldwide seroprevalence of HCV antibodies (anti-HCV) estimated at 3%
  - – Estimated 3-4 million persons infected in United States

Presentation

- Fatigue, nausea, anorexia, depression
- May be asymptomatic

Laboratory Tests

- Antibodies (anti-HCV) indicate exposure
- Detection of HCV RNA indicates virus persistence
- Liver biopsy performed to grade and stage disease and exclude other liver diseases

Natural History

- Acute infection is often subclinical; fulminant hepatitis rare
  - Persistent (chronic) infection occurs in 85% of infected persons
  - Defined as failure to clear virus in 6 months
  - Remaining 15% have self-limited infection

Treatment

- Drugs
  - Historically, standard therapy has been pegylated interferon-α in combination with ribavirin

  - Newer drugs are highly effective with fewer side effects
    - Protease inhibitors (e.g., simeprevir)
    - Nucleoside/nucleotide inhibitors (e.g., sofosbuvir) and nonnucleotide inhibitors

Prognosis

- Progressive disease, usually slow (over decades) and clinically silent; may lead to cirrhosis and liver failure
- Risk of hepatocellular carcinoma, usually in background of cirrhosis

MICROSCOPIC

Histologic Features

- Variably dense portal-based inflammatory infiltrates
  - Predominantly lymphocytes
  - Periportal interface activity
    - Lymphocytes disrupt limiting plate and surround nearby hepatocytes, causing hepatocyte injury and necrosis
- Scattered lobular collections of inflammatory cells ± acidophil bodies
- Mild bile duct injury ± lymphocytic infiltrate (Poulsen lesions)
- Mild, patchy steatosis
  - Greater degree of steatosis associated with genotype 3b
- Histologic features are scored; several grading/staging schemes available
  - Grade: Extent and severity of interface activity and lobular inflammation and injury
  - Stage: Extent of fibrosis
    - Progressive fibrosis begins in portal areas and extends outward in stellate fashion
- Acute infection rarely recognized clinically and rarely biopsied
  - Usually relatively mild lobular hepatitis
- Fibrosing cholestatic hepatitis C: Rare, severe variant in immunosuppressed patients

DIFFERENTIAL DIAGNOSIS

Hepatitis B Virus Infection

- Distinguished by serologic testing
- ± ground-glass hepatocytes

Autoimmune Hepatitis

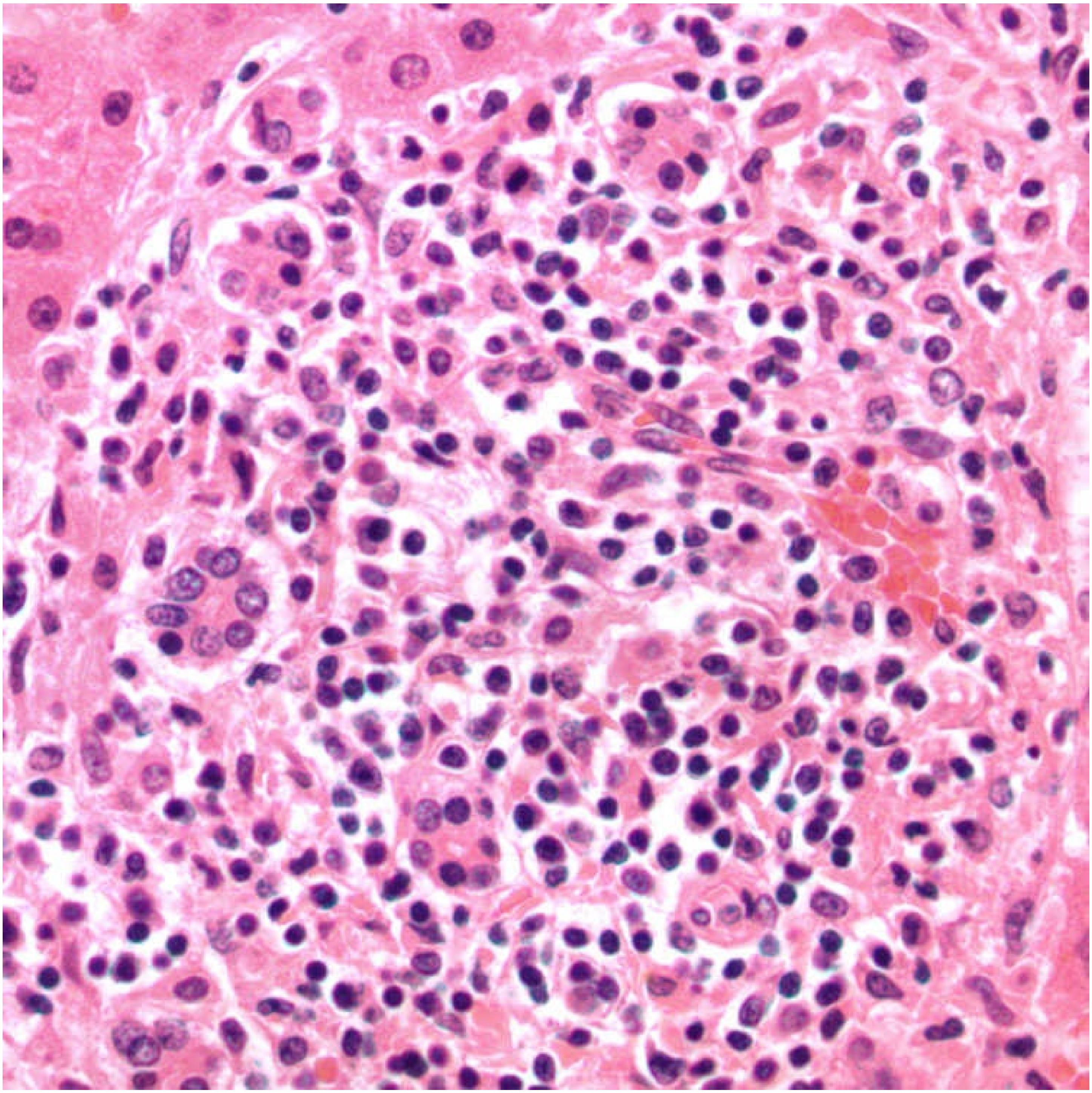
- Usually more severe hepatitis with more extensive interface activity and hepatocyte injury; prominent plasma cells
  - Distinguished by serologic testing for autoantibodies
  - False-positive anti-HCV can occur in autoimmune hepatitis, and autoantibodies may be expressed in HCV

Drug-Induced Hepatitis

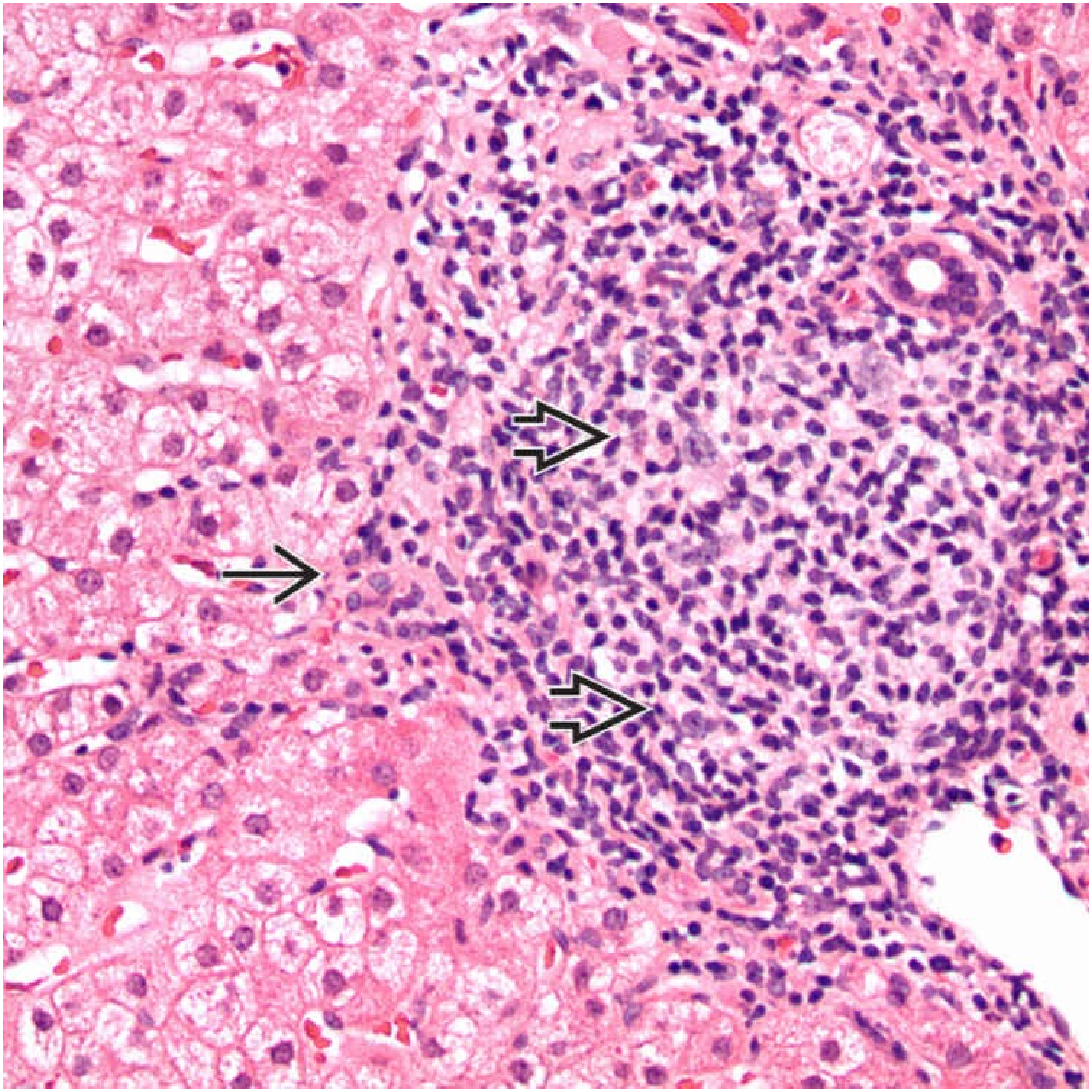
- Exclusion of HCV and identification of causative agent

Nonalcoholic Steatohepatitis

- Inflammation typically lobular rather than portal-based
- Fat usually zone 3 predominant rather than randomly distributed

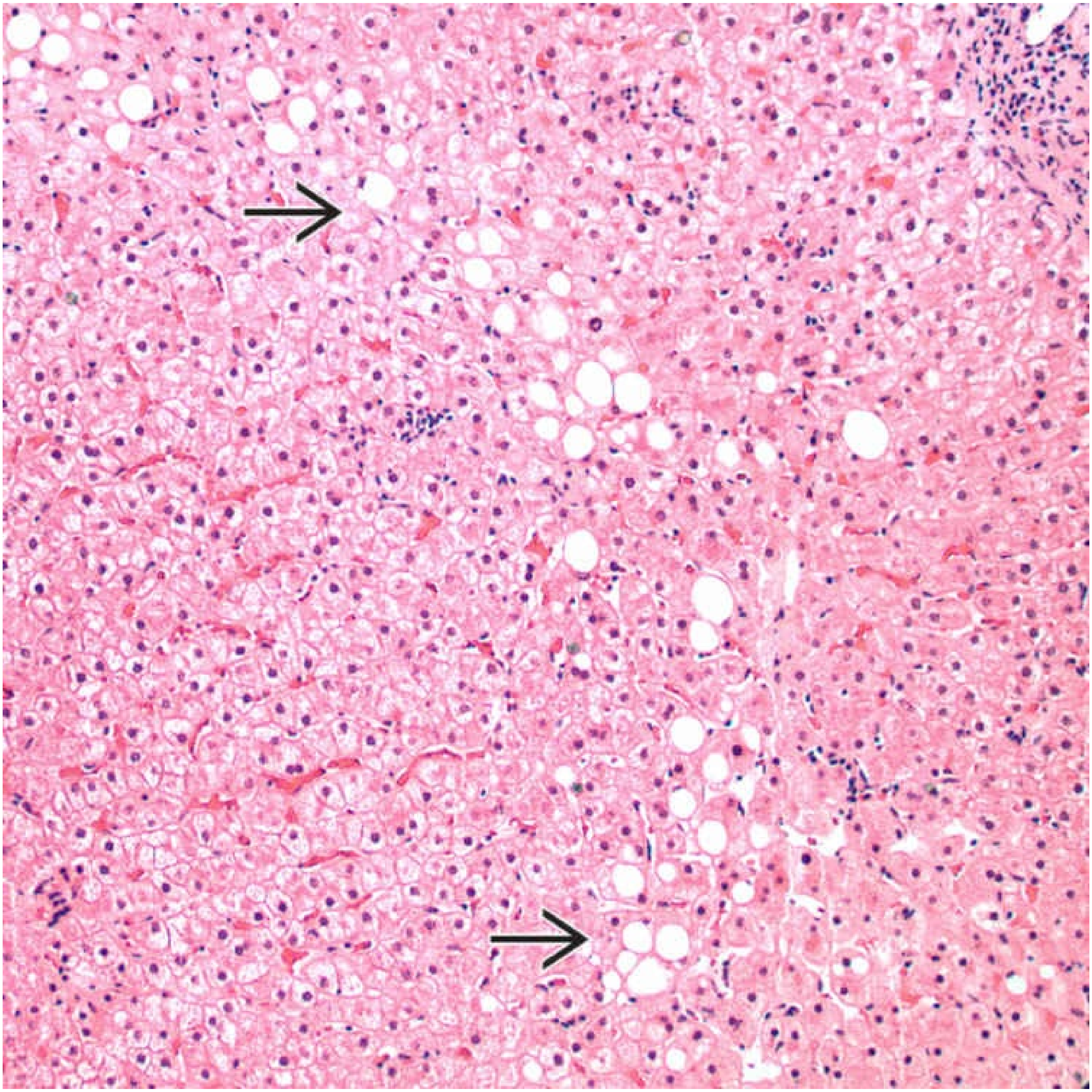


Portal Inflammation
The portal tract inflammatory cell infiltrate in HCV is generally composed of lymphocytes with occasional histiocytes and plasma cells. A few eosinophils and neutrophils may be seen but are generally not prominent. Lymphoid follicles with germinal centers may also be present.

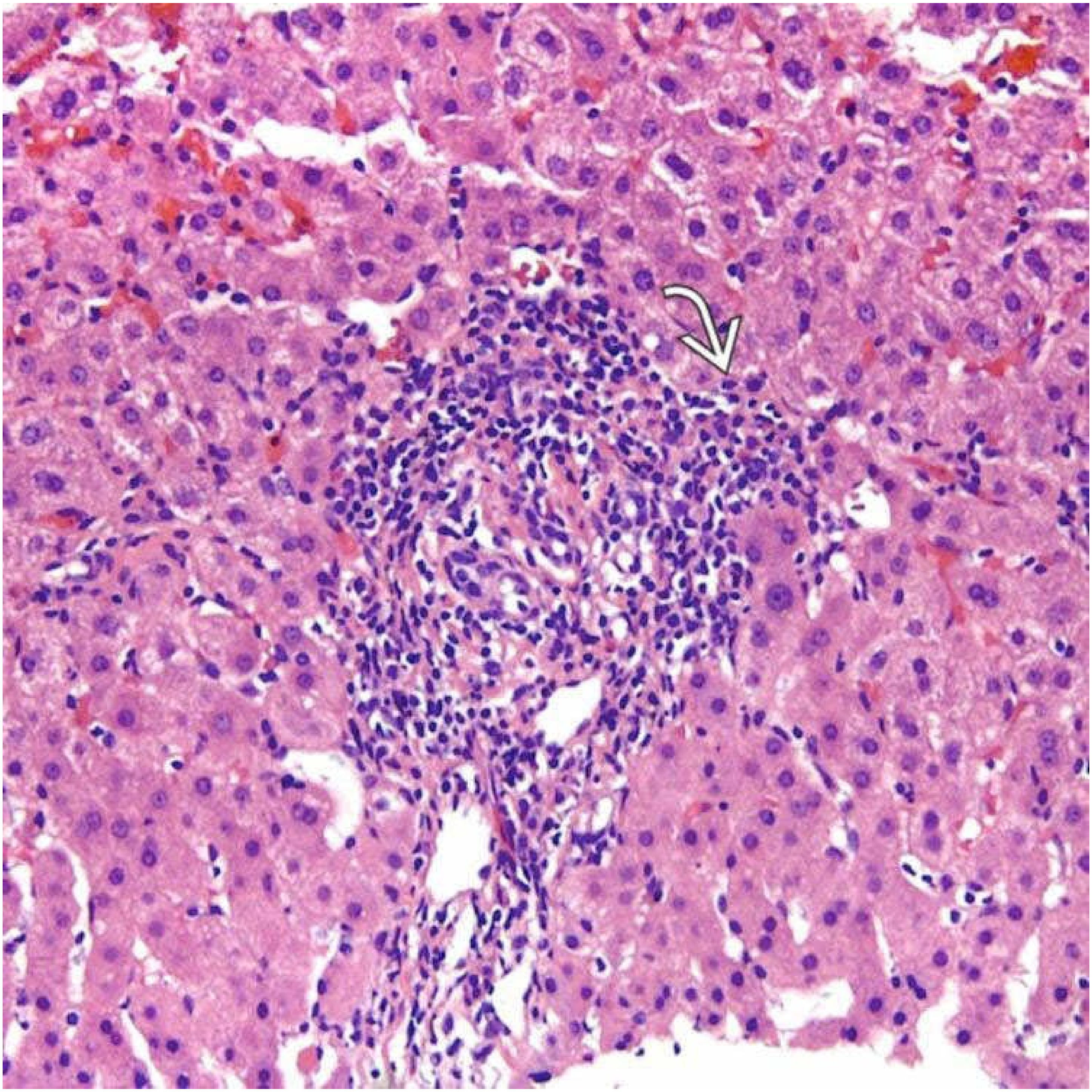


Portal Inflammation With Lymphoid Aggregate

An expanded portal tract with focal disruption of the limiting plate by interface activity → is seen in this case of HCV. Also present is a portal lymphoid aggregate ⇨ .

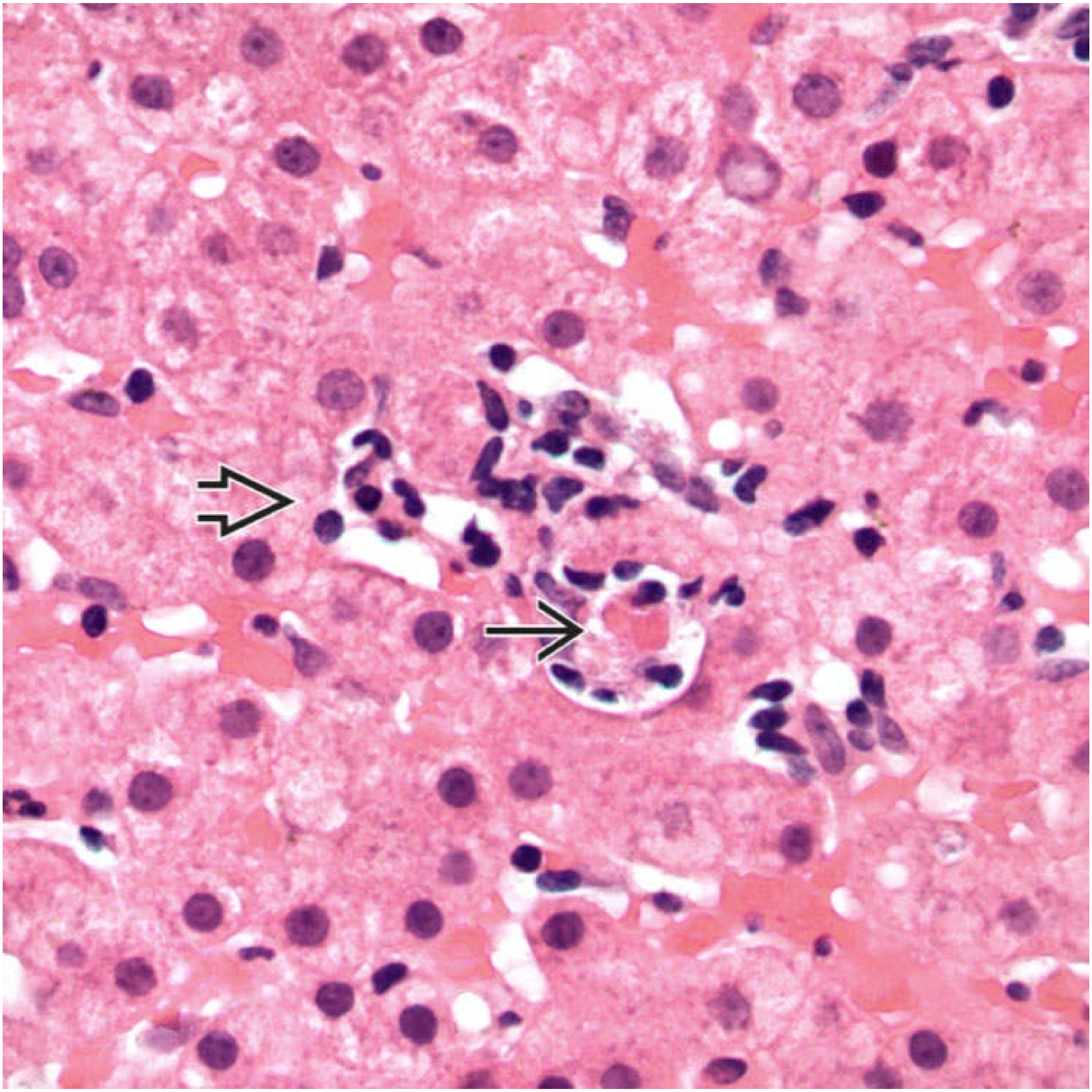


Steatosis
Mild, patchy steatosis → is common in chronic HCV infection. The steatosis typically lacks a zonal distribution, unlike fatty liver disease.



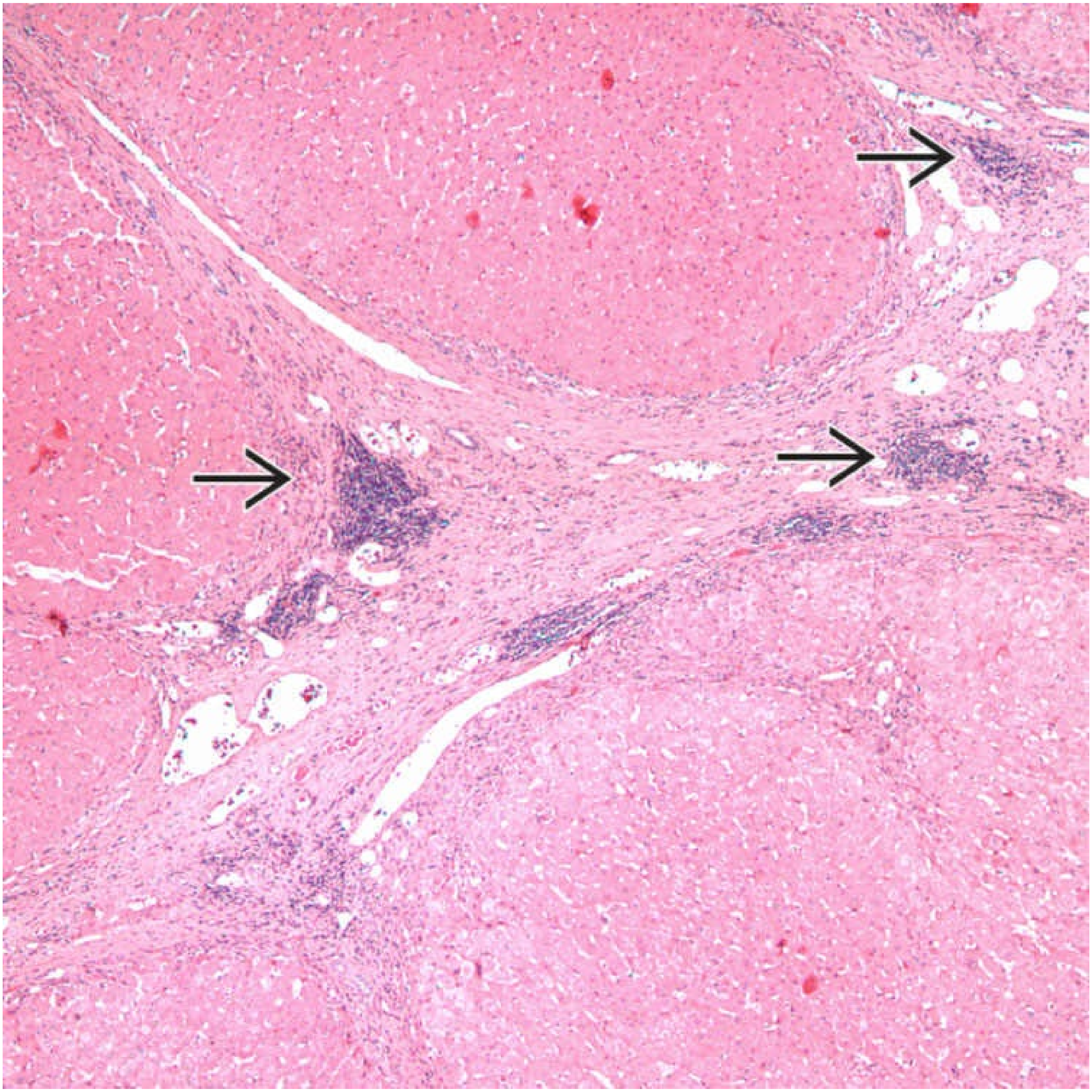
Portal and Lobular Inflammation

This case of HCV infection shows portal lymphocytic inflammation with some irregularity to the limiting plate, scant lobular inflammation, and spotty necrosis. This would typically be classified as a grade 2 (mild).

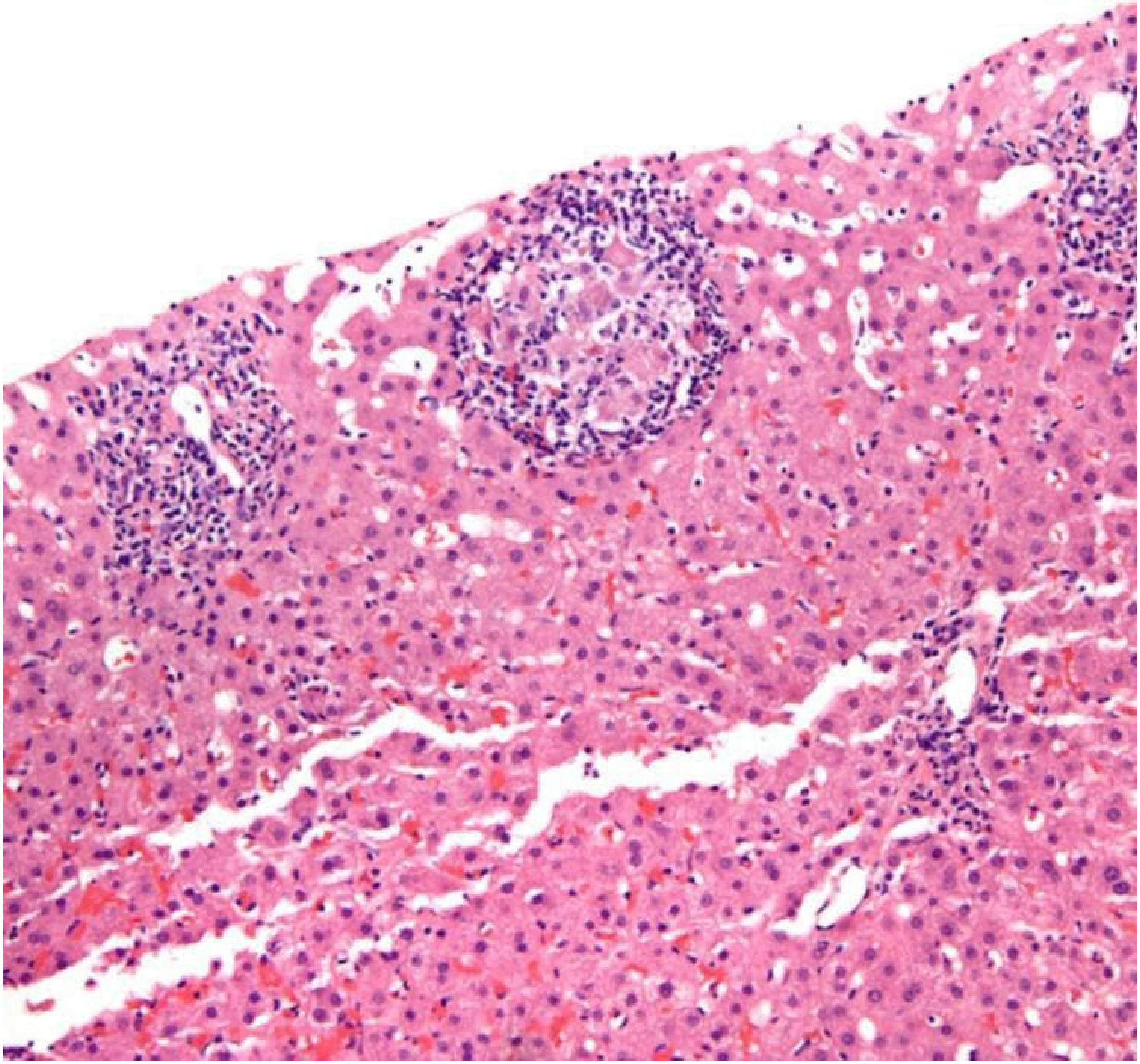


Spotty Necrosis

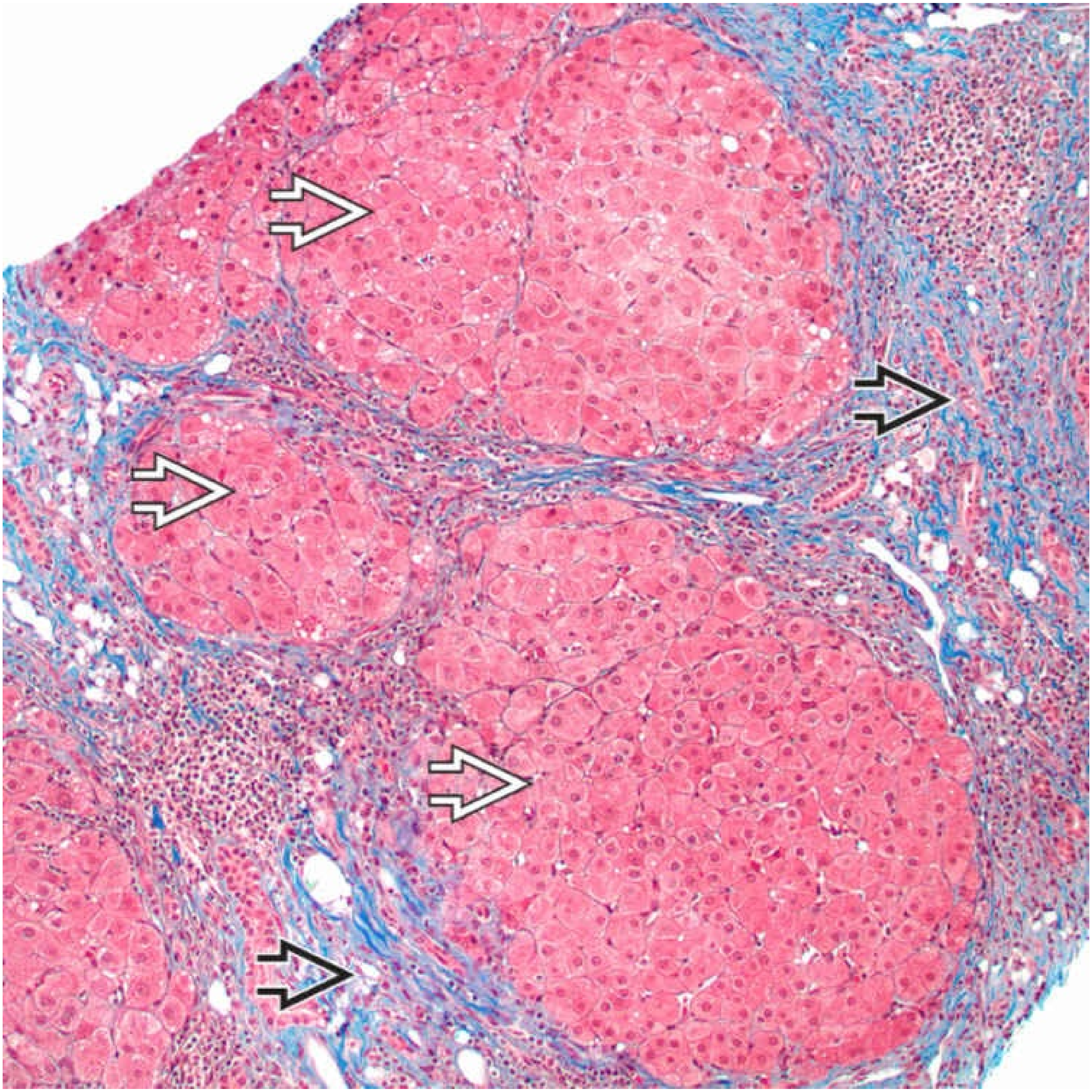
H&E demonstrates a focus of necroinflammatory activity in chronic hepatitis C, consisting of a collection of inflammatory cells ⇨ and a single acidophil body →, a.k.a. a Councilman body or necrotic hepatocyte. This change is also known as spotty necrosis.



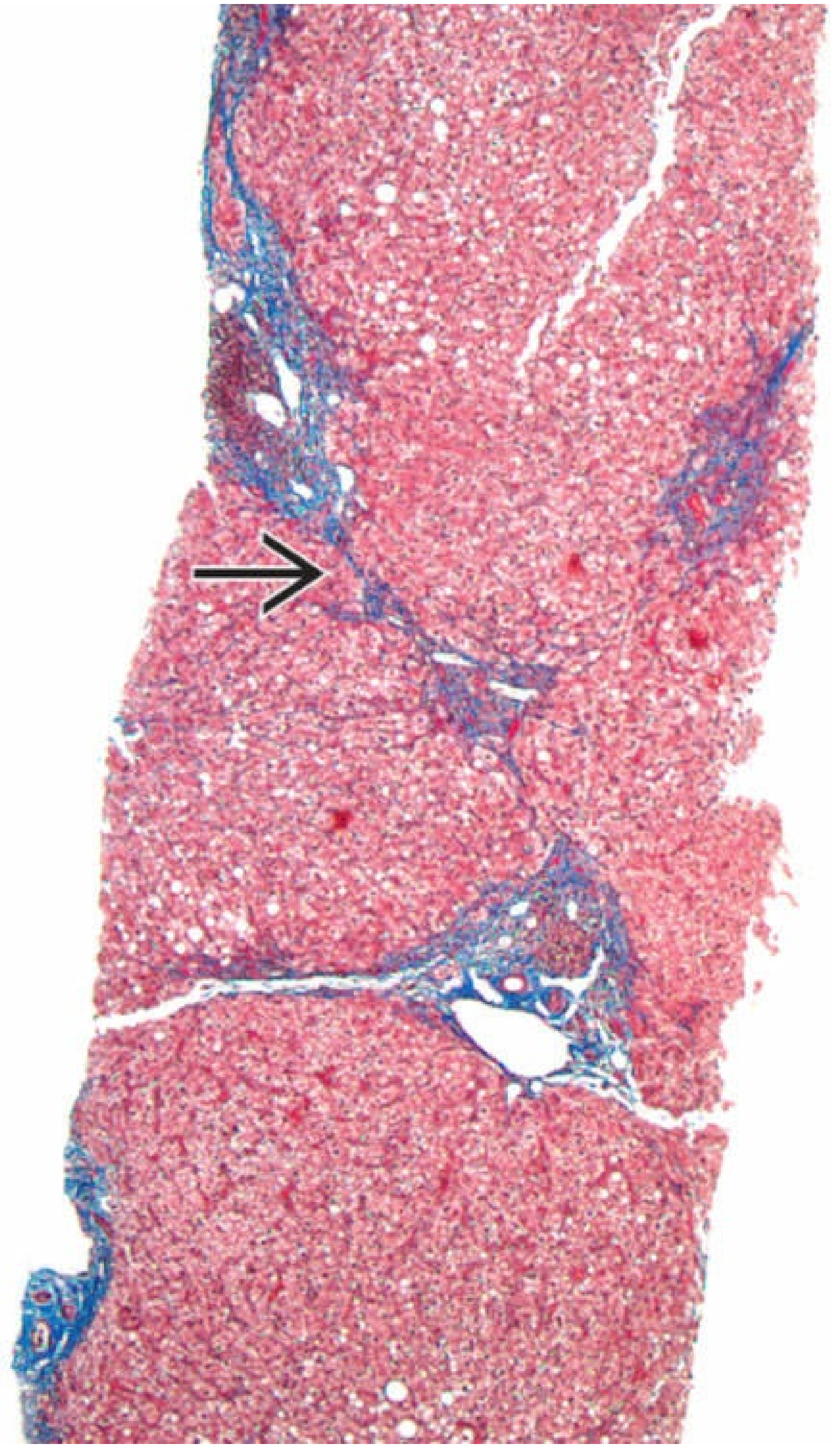
Lymphoid Aggregates
Scattered lymphoid aggregates → are present in portal areas and fibrous bands in this case of end-stage cirrhosis from HCV. These lymphoid aggregates should not be considered in determination of the grade.



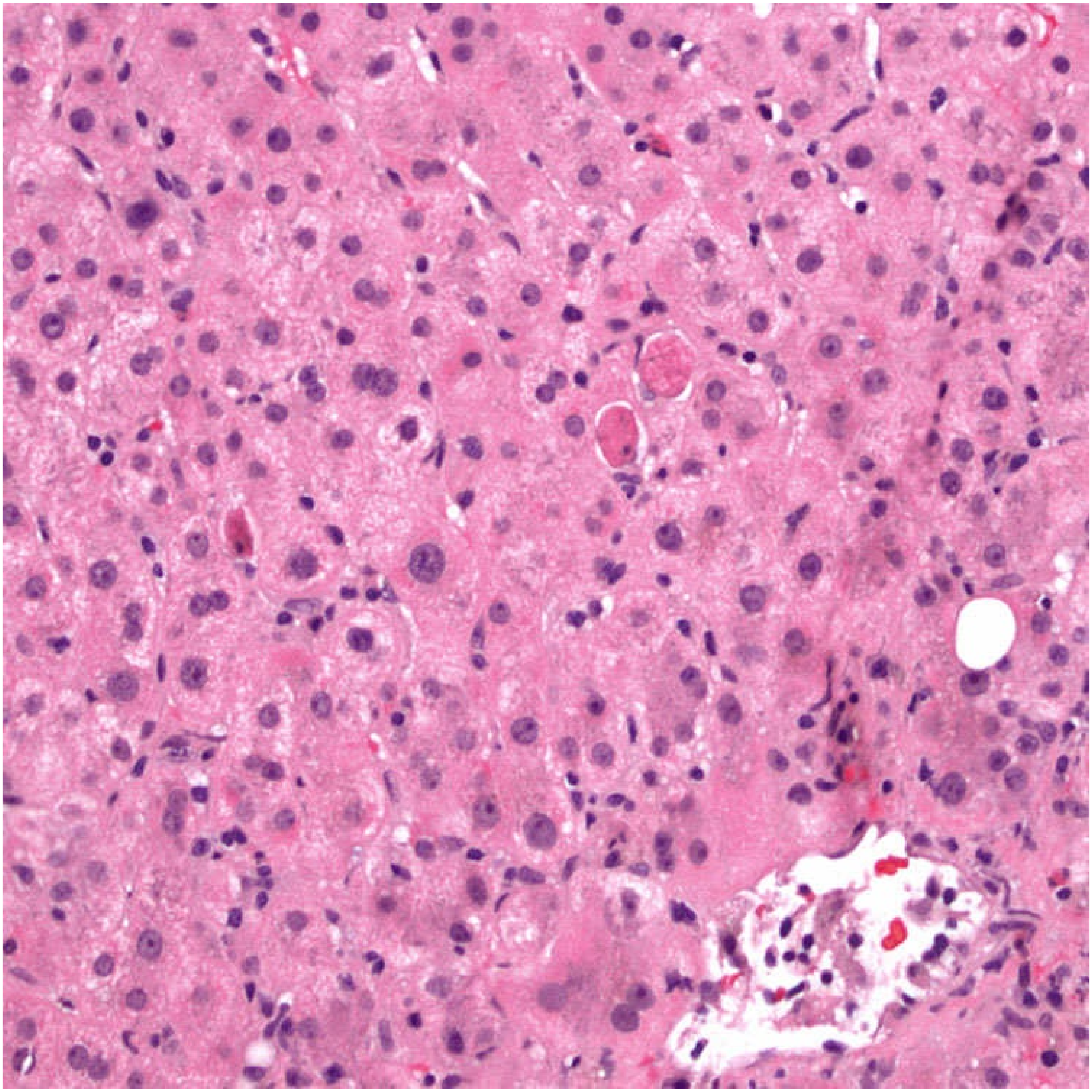
Granuloma
Occasional cases of hepatitis C show epithelioid, noncaseating granulomas. Other causes of granulomatous inflammation must be excluded in these cases as well.



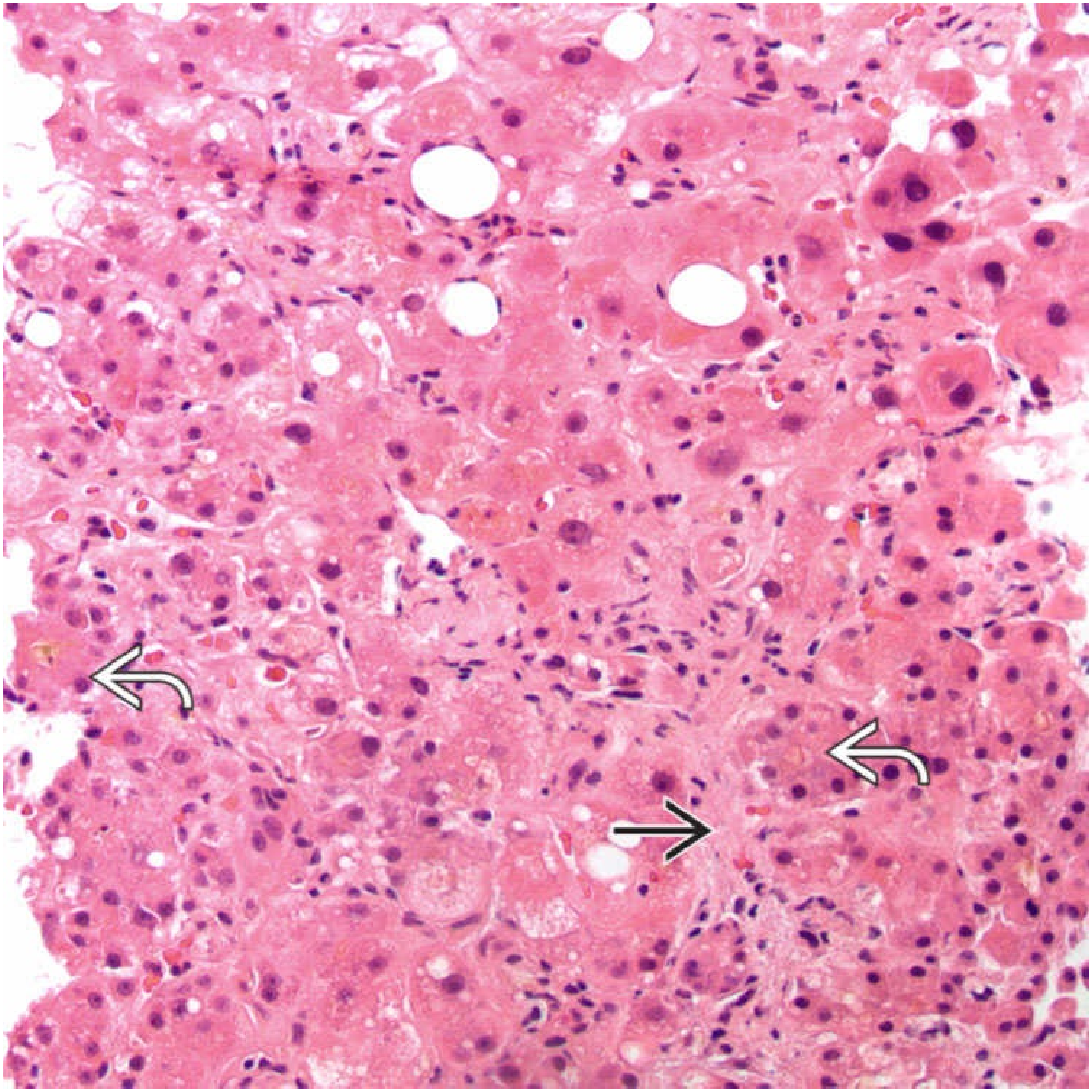
Cirrhosis
Trichrome stain demonstrates rounded, cirrhotic nodules in a background of fibrous stroma.
Cirrhosis represents the final stage of chronic HCV progression.



Bridging Fibrosis
Portal-based fibrosis extends outward from the portal tracts and, with progression, forms bridging fibrous septa → between portal tracts. Bridging fibrosis is typically classified as stage 3.

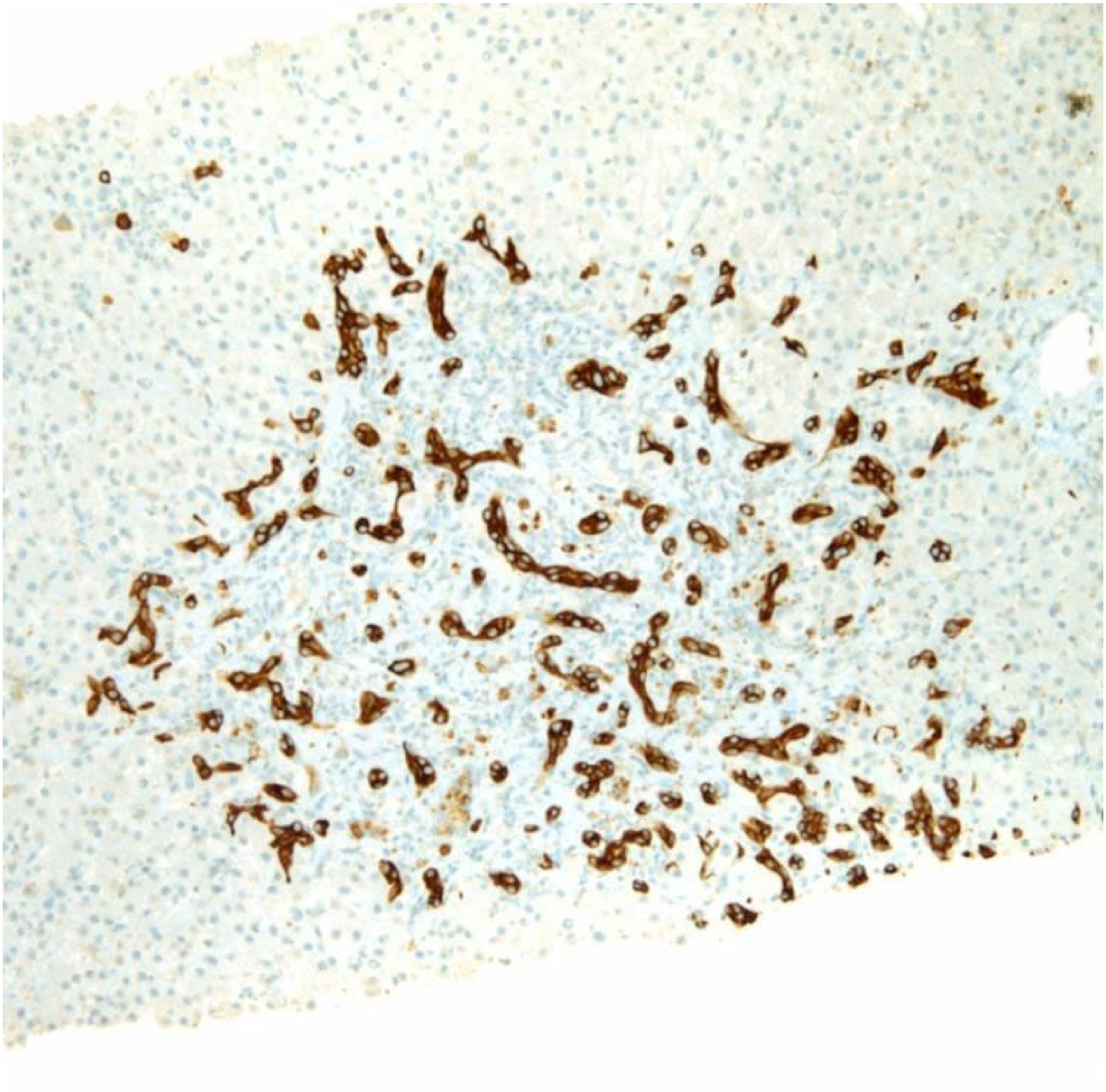


Transplant Recurrence
Numerous acidophil bodies and lobular inflammation are seen in a case of early recurrent hepatitis C after liver transplantation. Acute hepatitis C infection is rarely biopsied in native livers, but an early or acute phase is often recognized with hepatitis C recurrence after liver transplantation.



Fibrosing Cholestatic Variant

Cholestasis, inflammation, and fibrosis are present in this case of fibrosing cholestatic HCV. This variant is typically seen in the context of recurrent hepatitis C in a liver transplant recipient.



Fibrosing Cholestatic Variant
Cytokeratin 7 immunostain demonstrates the marked ductular reaction in fibrosing cholestatic hepatitis C.

SELECTED REFERENCES

1. Childs-Kean, LM, et al. Simeprevir and Sofosbuvir for Treatment of Chronic Hepatitis C Infection. *Clin Ther*. 2015. [ePub].
2. Wendt, A, et al. An update on the treatment of genotype-1 chronic hepatitis C infection: lessons from recent clinical trials. *Ther Adv Infect Dis*. 2013; 1(6):191–208.
3. Burra, P. Hepatitis C. *Semin Liver Dis*. 2009; 29(1):53–65.
4. Diepolder, HM. New insights into the immunopathogenesis of chronic hepatitis C. *Antiviral Res*. 2009; 82(3):103–109.
5. Lavanchy, D. The global burden of hepatitis C. *Liver Int*. 2009; 29(Suppl 1):74–81.

Epstein-Barr Virus

KEY FACTS

Terminology

- In liver, Epstein-Barr virus (EBV) may cause either hepatitis or posttransplant lymphoproliferative disorder (PTLD)

Etiology/Pathogenesis

- Member of herpesvirus family (human herpesvirus-4)
- Transmission via intimate contact, frequently with saliva of infected person

Clinical Issues

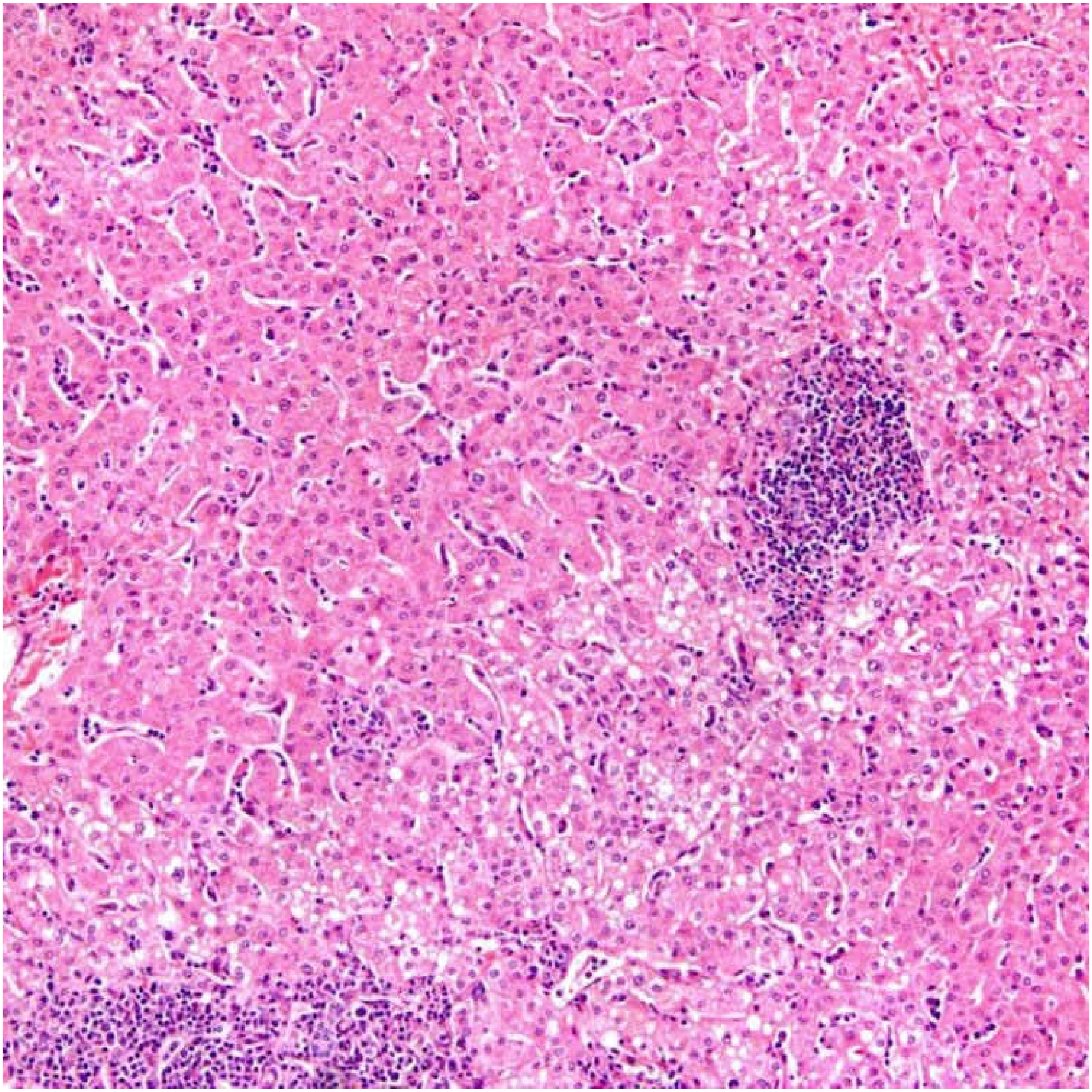
- EBV hepatitis
  - Usually represents liver involvement by infectious mononucleosis
  - Elevated serum transaminase, alkaline phosphatase, and bilirubin levels
  - Self limited in majority of cases
- EBV-associated lymphoproliferative disorders
  - In immunocompromised individuals due to uncontrolled EBV replication
  - Occurs in 1.0-2.8% of liver transplants
- Asymptomatic lifelong infection in > 90% of world adult population

Microscopic

- EBV hepatitis
  - Diffuse sinusoidal lymphocytic infiltration in Indian file or string of beads pattern
  - Mixed inflammatory cell infiltrates in portal tracts, consisting predominantly of lymphocytes
  - Scattered large and irregular (atypical) lymphocytes in sinusoids and portal tracts
- Hepatic PTLD
  - Morphology ranges from hepatitis-like to lymphoma

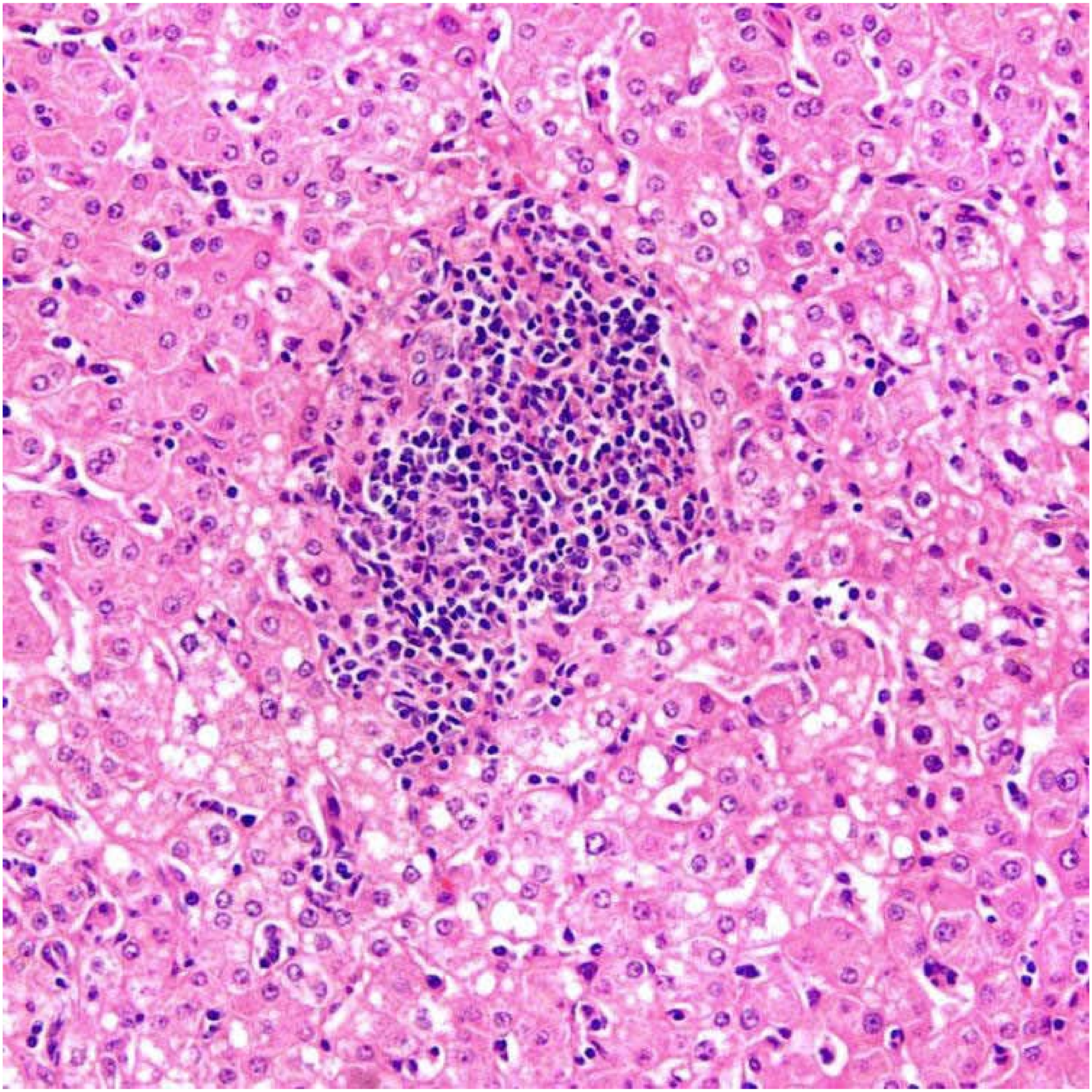
Ancillary Tests

• Detection of EBV early RNA (EBER) on tissue sections by in situ hybridization

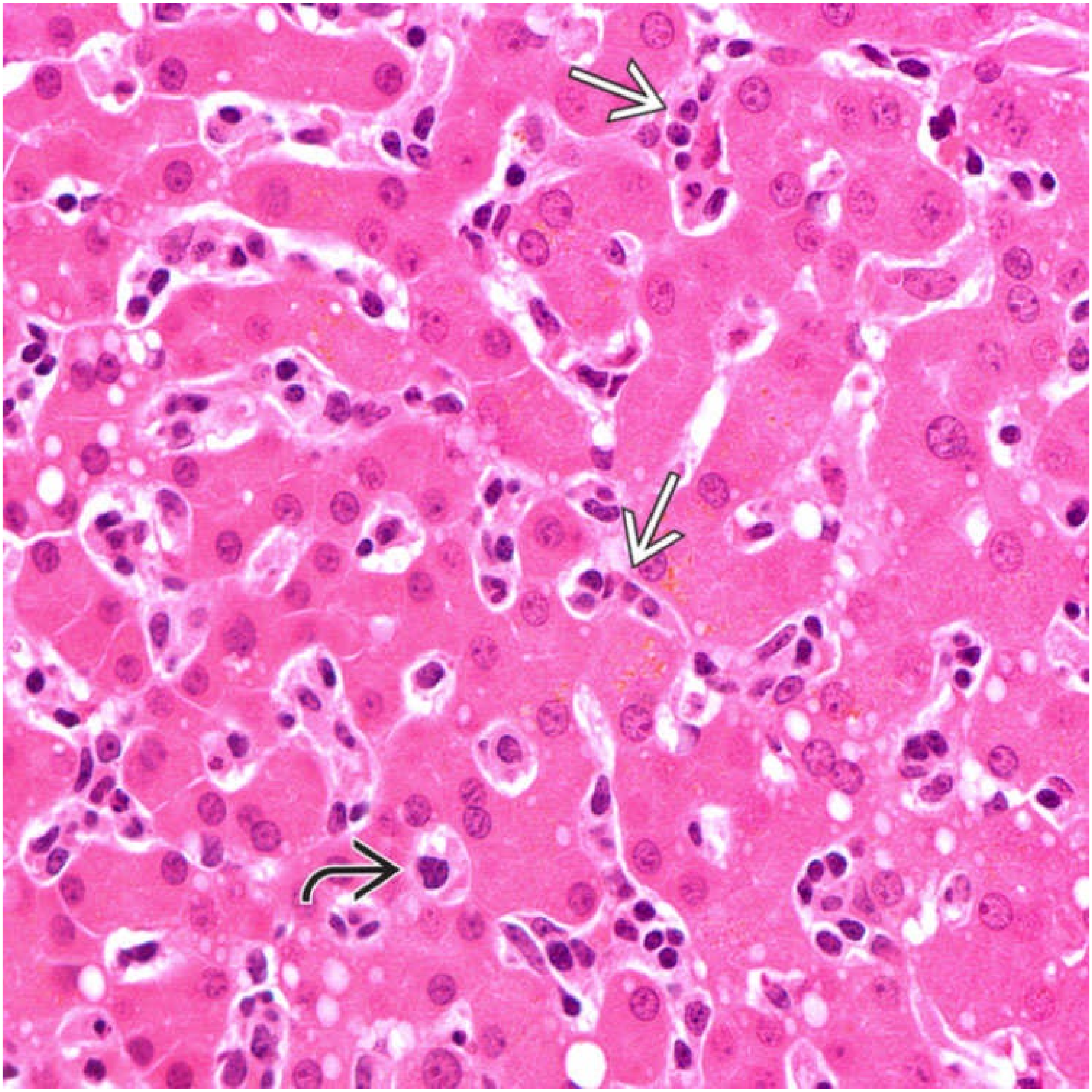


Portal and Lobular Inflammation

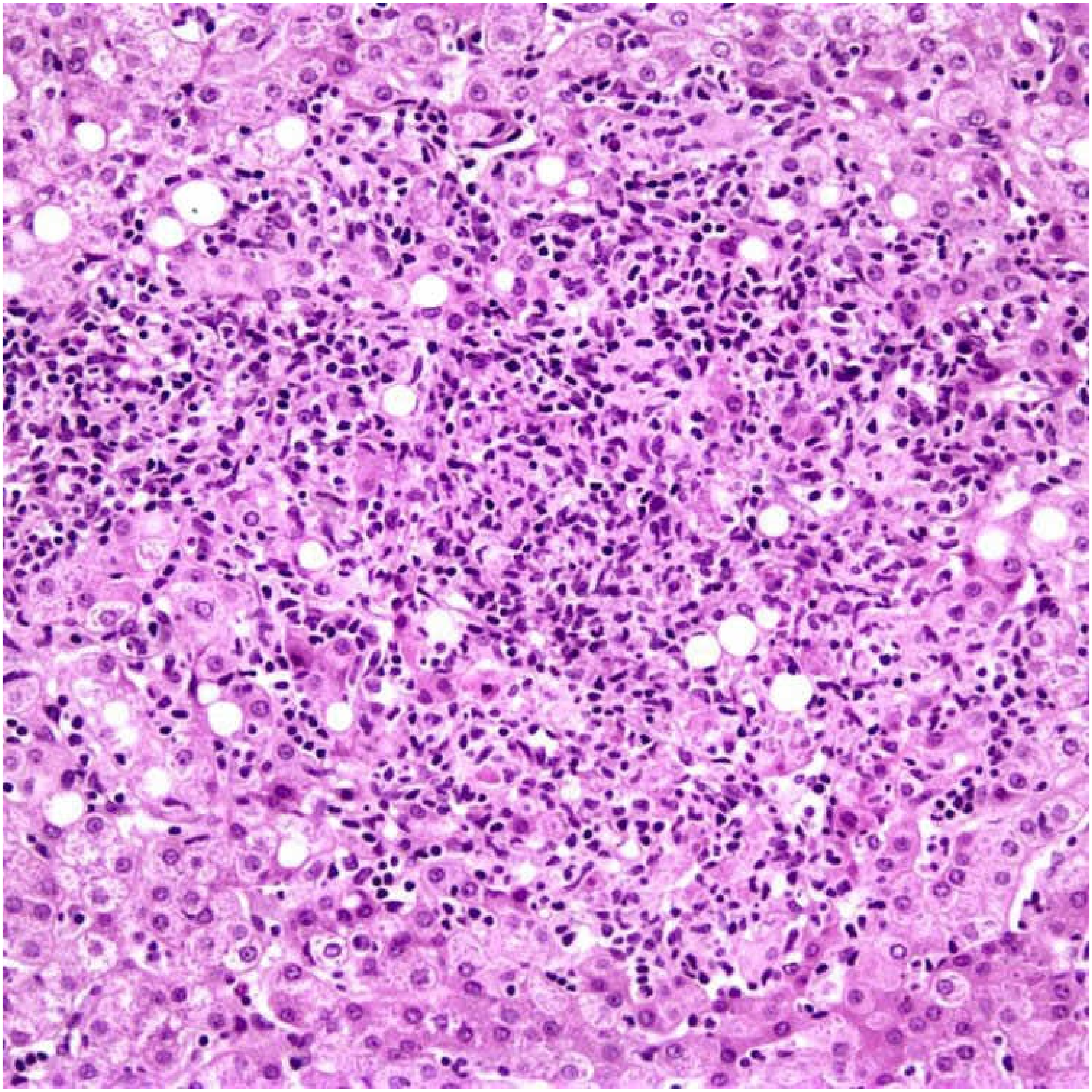
Epstein-Barr virus (EBV) hepatitis is characterized by portal and lobular inflammation consisting predominantly of lymphocytes. Prominent sinusoidal lymphocytes can be appreciated even at this low power. There is also mild steatosis, unrelated to EBV infection.



Portal and Sinusoidal Lymphocytosis
This case of EBV hepatitis shows portal and lobular lymphocytic infiltrates. Note the string of beads linear pattern of lymphocytes in the sinusoids.



String of Beads Sinusoidal Infiltrates
A characteristic finding of EBV hepatitis is a diffuse sinusoidal lymphocytic infiltrate with an Indian file or string of beads pattern ⇒. Occasional atypical lymphocytes ↷ are noted. Hemophagocytosis, which can be seen in EBV hepatitis, is not observed in this case.



Portal Inflammation
Occasionally, EBV hepatitis features a florid portal infiltrate consisting of lymphocytes (some of which may be atypical) and histiocytes. Note the surrounding sinusoidal lymphocytosis.

TERMINOLOGY

Abbreviations

• Epstein-Barr virus (EBV)

Definitions

• Infection by EBV

    - In liver, may cause either hepatitis or posttransplant lymphoproliferative disorder (PTLD)

ETIOLOGY/PATHOGENESIS

Infectious Agents

- Member of herpesvirus family (human herpesvirus-4)
    - Double-stranded DNA virus
- Transmission via intimate contact, frequently with saliva of infected person
    - Infection begins in oropharyngeal lymphoid tissues, particularly tonsils
    - Viral envelop glycoprotein binds to CD21 (CR2) on B lymphocytes

CLINICAL ISSUES

Epidemiology

- New infection typically occurs during adolescence or young adulthood in developed countries
    - Infectious mononucleosis 35-50% of time
- Typically occurs in 1st few years of life in developing countries with universal seroconversion by 3-4 years of age
    - Usually asymptomatic
- Asymptomatic lifelong infection in > 90% of world adult population
- Dormant or latent in memory B lymphocytes
    - Can be reactivated
    - Commonly found in saliva

Presentation

- Infectious mononucleosis
    - Incubation time of 4-6 weeks
    - Fever, fatigue, malaise, sore throat, arthralgia, jaundice, lymphadenopathy, splenomegaly, and hepatomegaly
    - Self-limited, usually resolves in 1-2 months
- EBV hepatitis
    - Usually represents liver involvement by infectious mononucleosis
    - Seen in immunocompetent and immunocompromised individuals
    - Hepatomegaly seen in 10-15% of patients
    - Jaundice seen in ~ 5% of patients
    - Elevated serum transaminase, alkaline phosphatase, and bilirubin levels
- EBV-associated lymphoproliferative disorders
    - In immunocompromised individuals due to uncontrolled EBV replication
        - Occurs in 1.0-2.8% of liver transplants
        - Accounts for > 50% of all tumors in children and ~ 15% of all tumors in adults following liver transplantation
        - > 80% of cases occur in the first 2 years after transplantation

- – Host origin in majority of cases, rarely donor origin
- – Negative EBV status at transplantation and heavy immunosuppression for treatment of rejection are major risk factors

Laboratory Tests

- Peripheral lymphocytosis with > 10% atypical lymphocytes
  - Serologic studies
  - ○ Positive monospot test for heterophile antibody
  - ○ Primary infection
  - – Elevated IgM titer to viral capsid antigen (VCA)
  - – Rising IgG titer to VCA
  - – Absent antibody to nuclear antigen (EBNA)
  - – Positive antibody to early antigen (EBEA)

○ Reactivation of latent infection

– Elevated antibody titer to EBEA in presence of antibody to EBNA

○ Past infection

– Presence of antibodies to both VCA and EBNA

- Molecular tests
  - ○ Detection of viral DNA in peripheral blood by PCR
  - ○ Detection of EBV early RNA (EBER) on tissue sections by in situ hybridization
  - ○ Gene arrangement for immunoglobulins and T-cell receptors for cases suspicious for PTLD
- Immunohistochemistry
  - ○ Detection of EBV-latent membrane proteins on tissue sections
  - ○ Immunohistochemical stains for B- and T-cell markers as well as κ and λ light chains in cases suspicious for PTLD

Treatment

- EBV hepatitis
  - ○ Symptomatic &/or supportive treatment
  - ○ Use of corticosteroids and antiviral agents remains controversial
- PTLD lacks general treatment paradigm due to disease heterogeneity
  - ○ Restoration of cellular immunity
    - – Reduction of immunosuppression
    - – Interferon-α
  - ○ Antitumor therapies
    - – Surgery/radiation for localized disease
    - – Chemotherapy
    - – Rituximab for CD20(+) disease
    - – Anti-IL-6 antibody
  - ○ Antiviral agents

Prognosis

- Self-limited in majority of EBV hepatitis cases
  - Does not progress to chronic hepatitis or cirrhosis
- Serious complications of EBV hepatitis occur in < 5% of cases
  - Fulminant hepatic failure
  - Splenic rupture
  - Hemolytic anemia
  - Hemophagocytic syndrome
  - Guillain-Barré syndrome
  - Malignancies
- PTLD
  - Varies from benign lymphoproliferative lesion to aggressive lymphoma
  - Pediatric patients tend to develop lesions with more favorable histology and have better survival rate in comparison with adults

MACROSCOPIC

General Features

- Hepatomegaly
- Liver mass in patients with PTLD

MICROSCOPIC

Histologic Features

- EBV hepatitis
  - Diffuse sinusoidal lymphocytic infiltration in Indian file or string of beads pattern
  - Moderate to marked mixed inflammatory cell infiltrates in portal tracts, consisting predominantly of lymphocytes
    - Scattered large and irregular (atypical) lymphocytes in sinusoids and portal tracts
    - Scattered foci of interface activity
  - Focal lobular disarray with focal hepatocyte ballooning and scattered acidophil bodies
  - Small noncaseating epithelioid granulomas (microgranulomas) or fibrin-ring granulomas in lobules
  - Varying degree of steatosis with no particular zonal distribution
  - Cholestasis not prominent
  - Mild bile duct damage
    - No significant ductular reaction
  - Focal endophlebitis

- No fibrosis

- Hepatic PTLD
  - 3 major disease categories
  - Early lesions characterized by reactive plasmacytic hyperplasia or infectious mononucleosis-like lesions
    - Mixed mononuclear cell infiltrates in portal tracts, including small- and medium-sized lymphocytes, atypical lymphocytes, immunoblasts, and plasma cells
    - Sinusoidal lymphocytic infiltration similar to that seen in EBV hepatitis
    - Infiltrative lymphocytes are predominantly B cells, in contrast to predominantly T cells in EBV hepatitis
  - Polymorphic PTLD characterized by mixed lymphoplasmacytic proliferation
    - More frequent atypical lymphoid cells (blast forms)
    - Either polyclonal or monoclonal
  - Monomorphic PTLD is same as lymphoma seen in immunocompetent hosts
    - Classified according to standard lymphoma classification
    - > 80% derive from B-cell proliferation; most common subtype is diffuse large B-cell lymphoma
    - Rare subtypes include Burkitt or Burkitt-like lymphoma, plasma cell myeloma, peripheral T-cell lymphoma, γ/δ T-cell lymphoma, T-/NK-cell lymphoma, Hodgkin lymphoma, and Hodgkin lymphoma-like PTLD
    - Proliferation of neoplastic lymphoid cells form solitary mass or multiple masses
    - Diffuse infiltration of portal tracts &/or sinusoids by neoplastic lymphoid cells less common
    - Destruction of normal hepatic architecture

DIFFERENTIAL DIAGNOSIS

Hepatic Involvement by Leukemia

- Sinusoidal and portal infiltration by monotonous lymphoid or myeloid cells
- Flow cytometry and immunohistochemistry are helpful

Hepatosplenic T-Cell Lymphoma

- Sinusoidal infiltration by monotonous, medium-sized cytotoxic T cells expressing γ/δ receptor
- Characteristic CD3(+), CD4(-), and CD8(-) immunophenotype
- Clonal γ/δ T-cell receptor rearrangement
- Clonal α/β T-cell receptor rearrangement seen in occasional cases
- Presence of isochromosome 7q

Acute Cellular Rejection

- More pronounced bile duct damage &/or endophlebitis
- Less prominent sinusoidal lymphocytic infiltrates
- Negative EBER by in situ hybridization

Recurrent Hepatitis C Post Transplant

- Less prominent sinusoidal lymphocytic infiltrates
- Portal lymphoid aggregates
- Portal and periportal fibrosis
- Negative EBER by in situ hybridization

CMV Hepatitis

- Occasionally produces mononucleosis-like pattern
- Intranuclear and intracytoplasmic viral inclusions ± microabscesses
- Immunohistochemistry and in situ hybridization are helpful

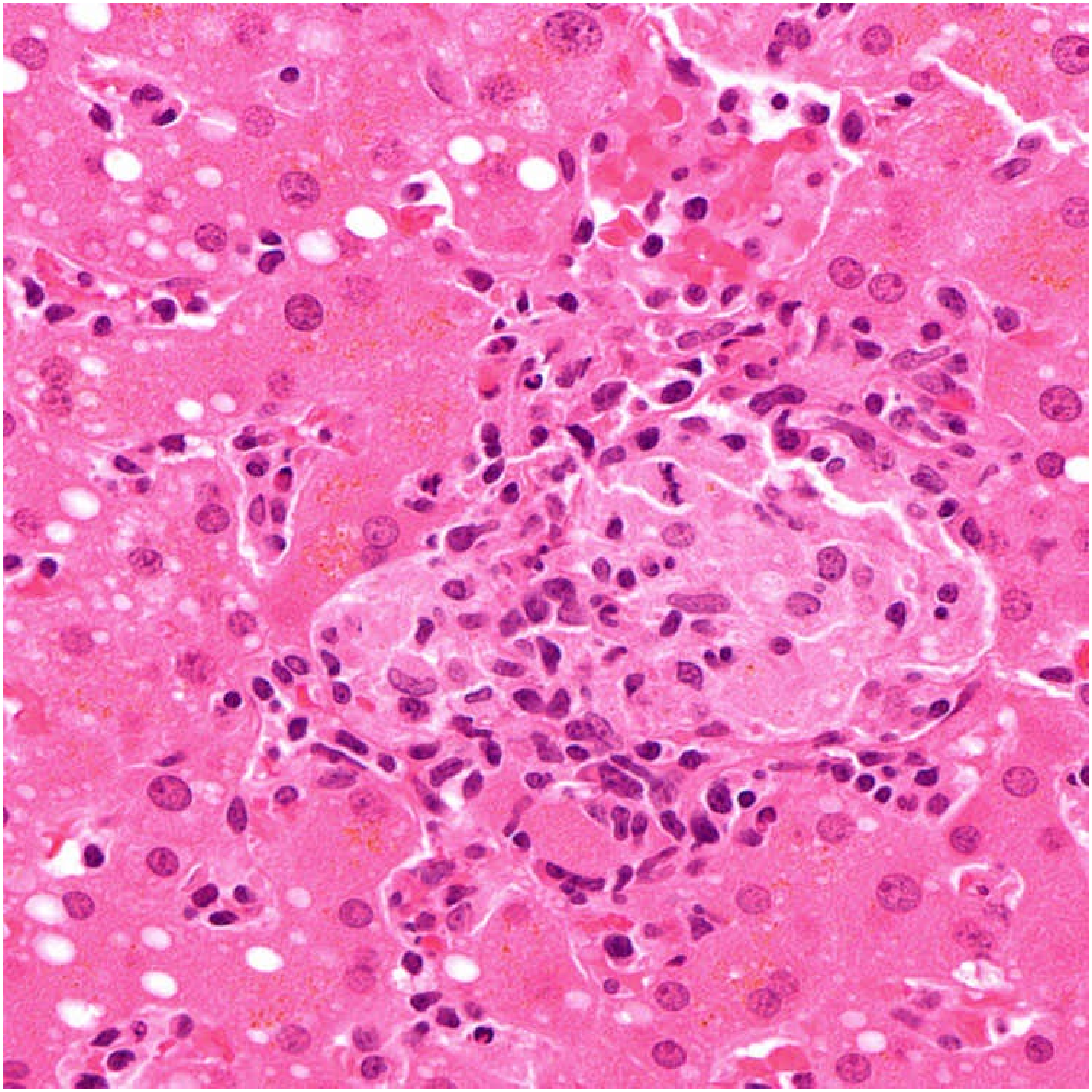
Drug-Induced Hepatitis

- May produce mononucleosis-like pattern
- History of drug use (phenytoin, sulfonamides, dapsone, minocycline, etc.)
- May show confluent lobular necrosis occasionally
- Portal eosinophils may be more prominent
- Cholestasis may be more pronounced
- Negative EBER by in situ hybridization

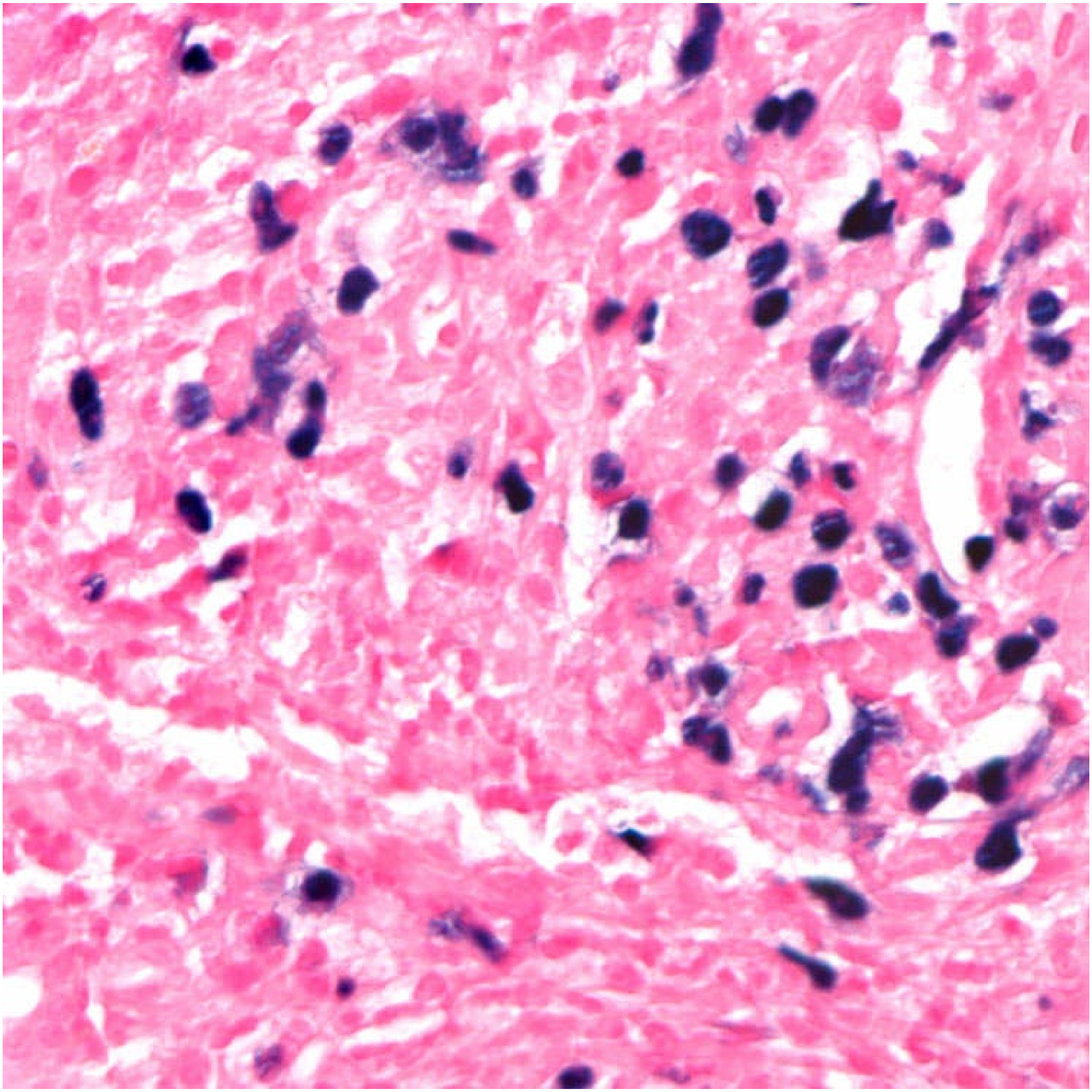
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Elevated liver function tests in patients with symptoms and signs of infectious mononucleosis

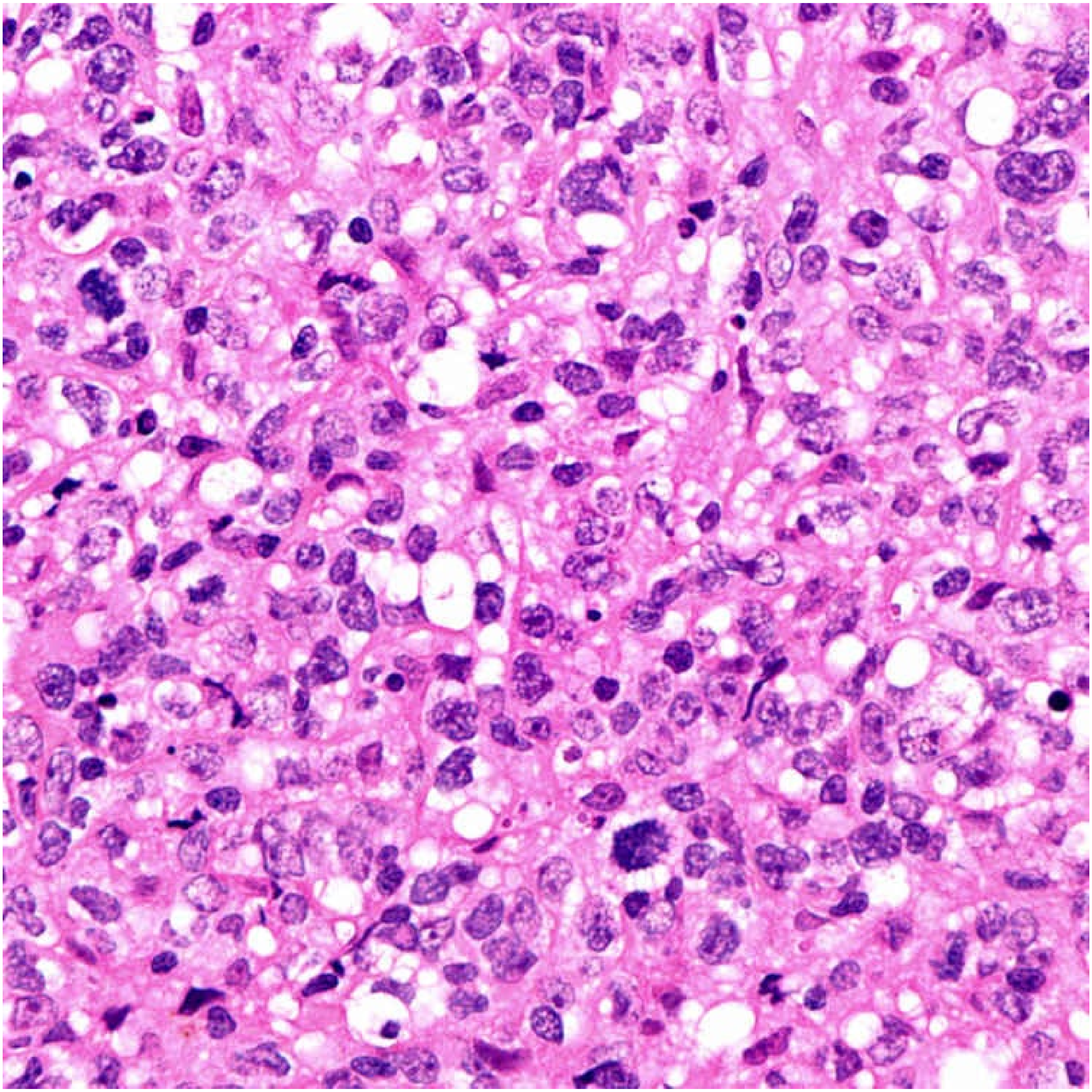


Epithelioid Granuloma
EBV hepatitis can produce small noncaseating epithelioid granulomas (microgranulomas) in the lobules. Granulomas can also be found in the portal tracts in cases of EBV hepatitis.

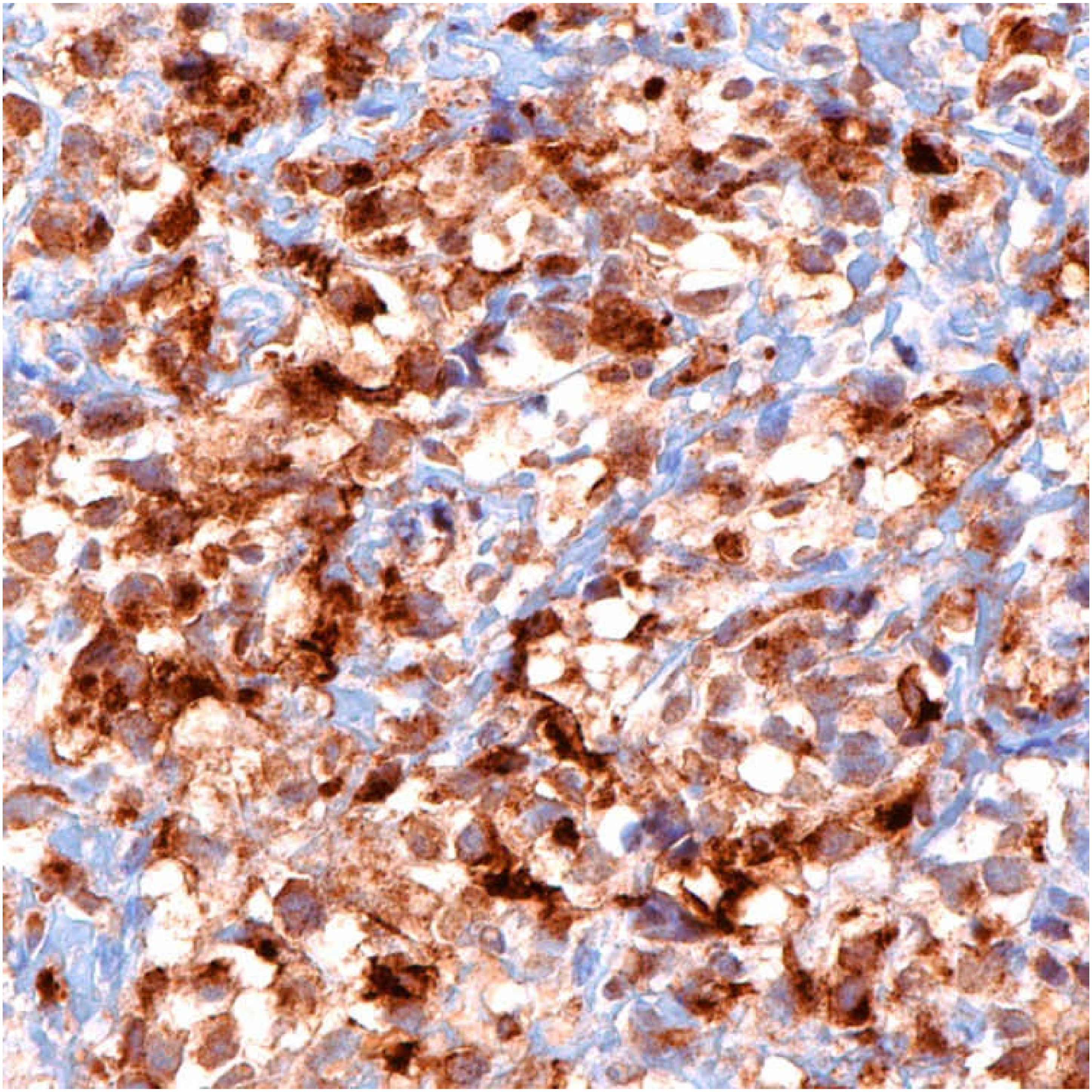


EBV RNA

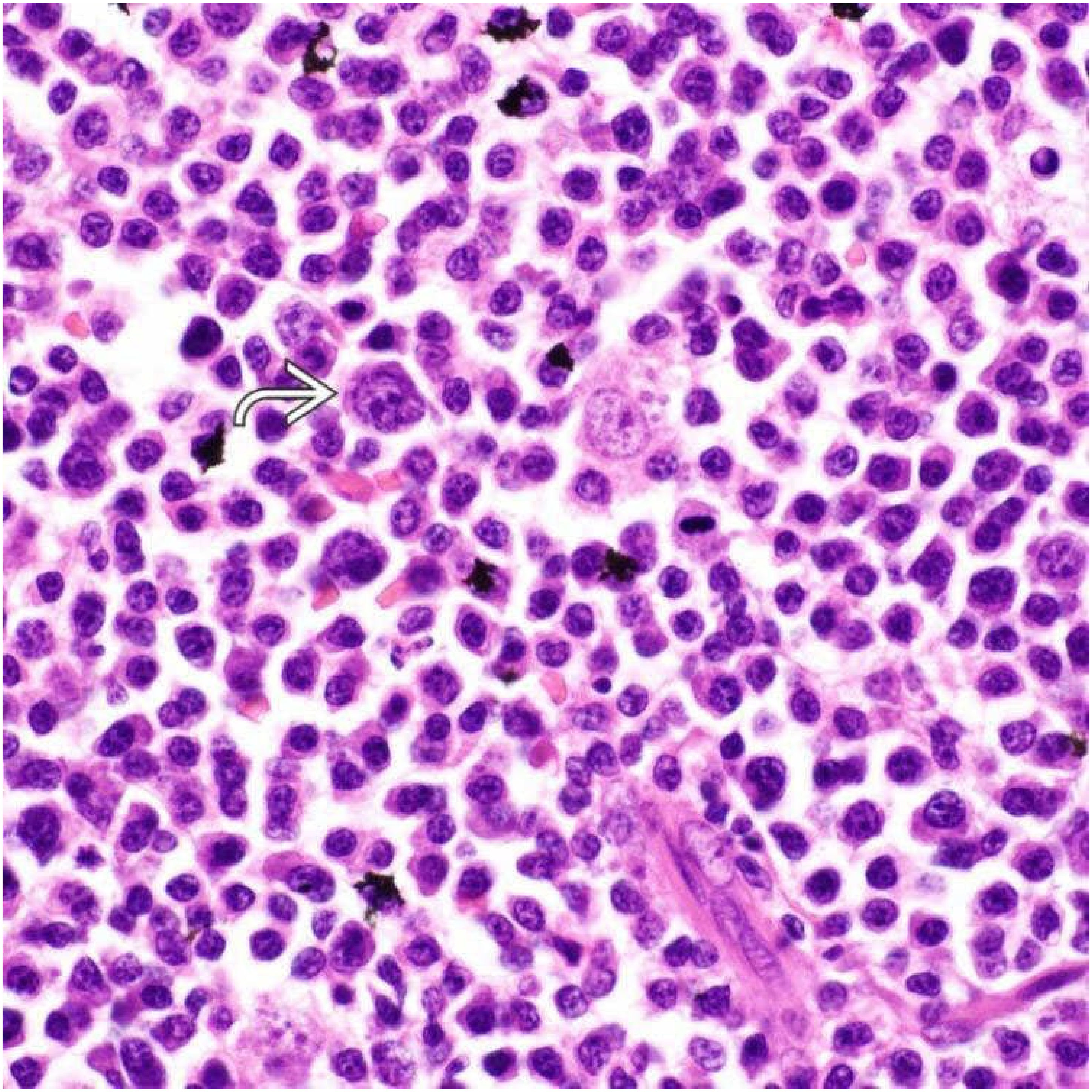
In situ hybridization shows that infiltrative lymphocytes in the portal tracts and sinusoids are positive for EBV early RNA in EBV hepatitis. Immunostain for EBV-latent membrane proteins is not a sensitive detection method.



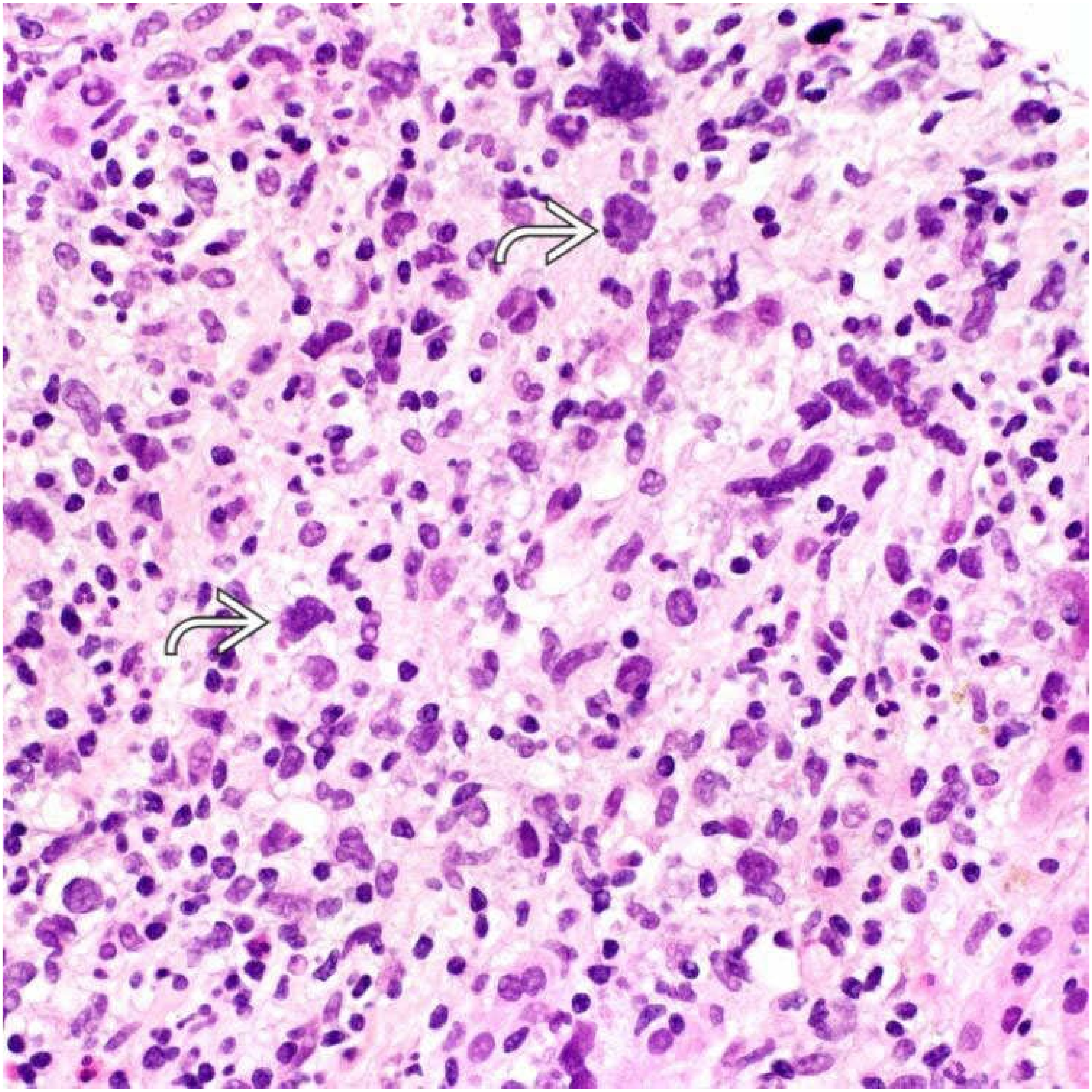
EBV-Associated Posttransplant Lymphoproliferative Disorder
This photomicrograph shows a case of EBV-associated diffuse large B-cell lymphoma in a liver allograft [monomorphic posttransplant lymphoproliferative disorder (PTLD)].



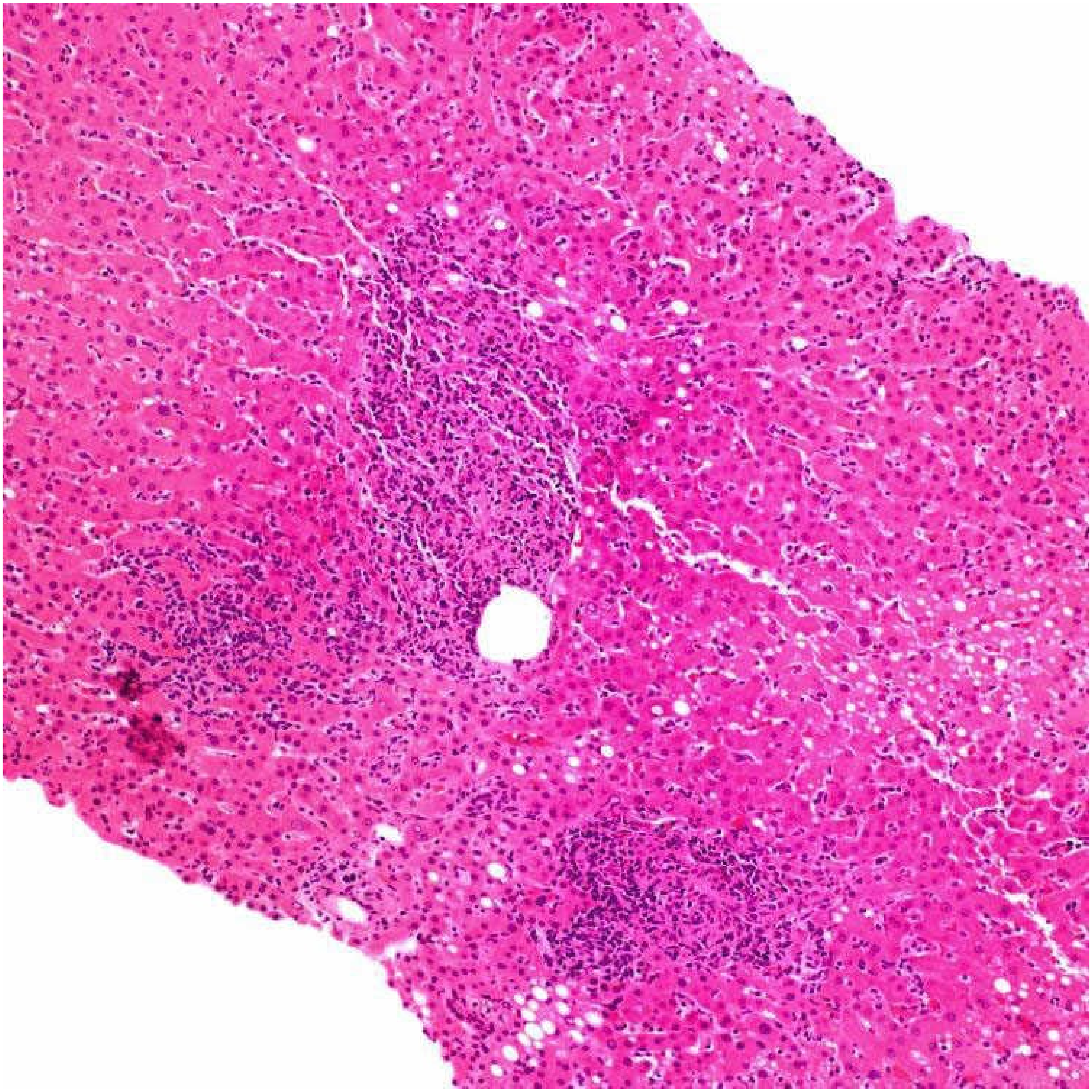
EBV-Latent Membrane Proteins
This immunohistochemical stain for EBV-latent membrane proteins shows positive cytoplasmic staining in neoplastic cells in a case of hepatic monomorphic PTLD (diffuse large B-cell lymphoma) shown in the left panel. This stain is not a sensitive marker for EBV hepatitis.



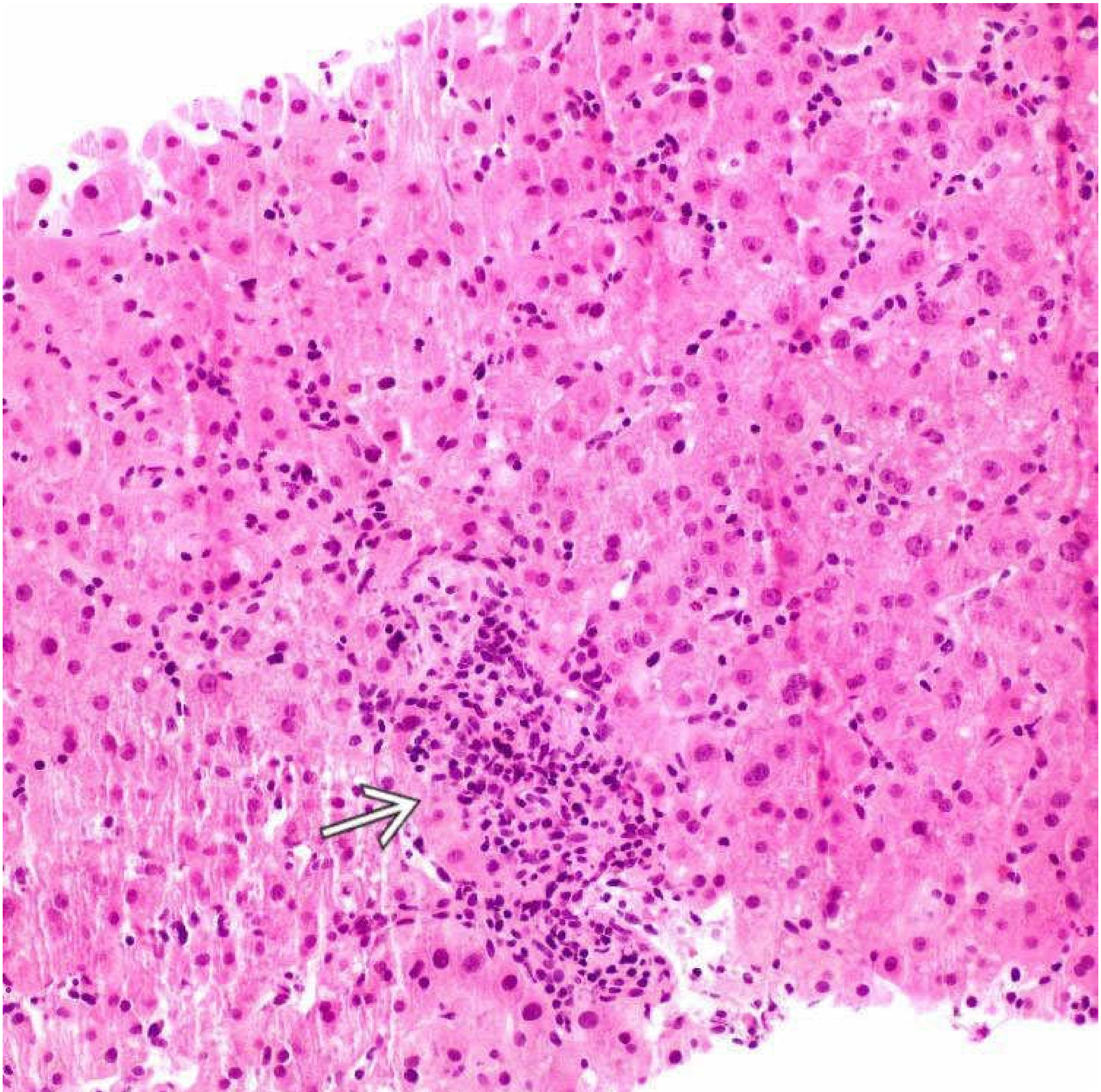
EBV-Associated Posttransplant Lymphoproliferative Disorder
This case of EBV-associated polymorphic PTLD is characterized by diffuse proliferation of small lymphoid and plasmacytoid cells. Occasional larger immunoblastic cells are present ⇗. Immunostains demonstrated λ light chain restriction.



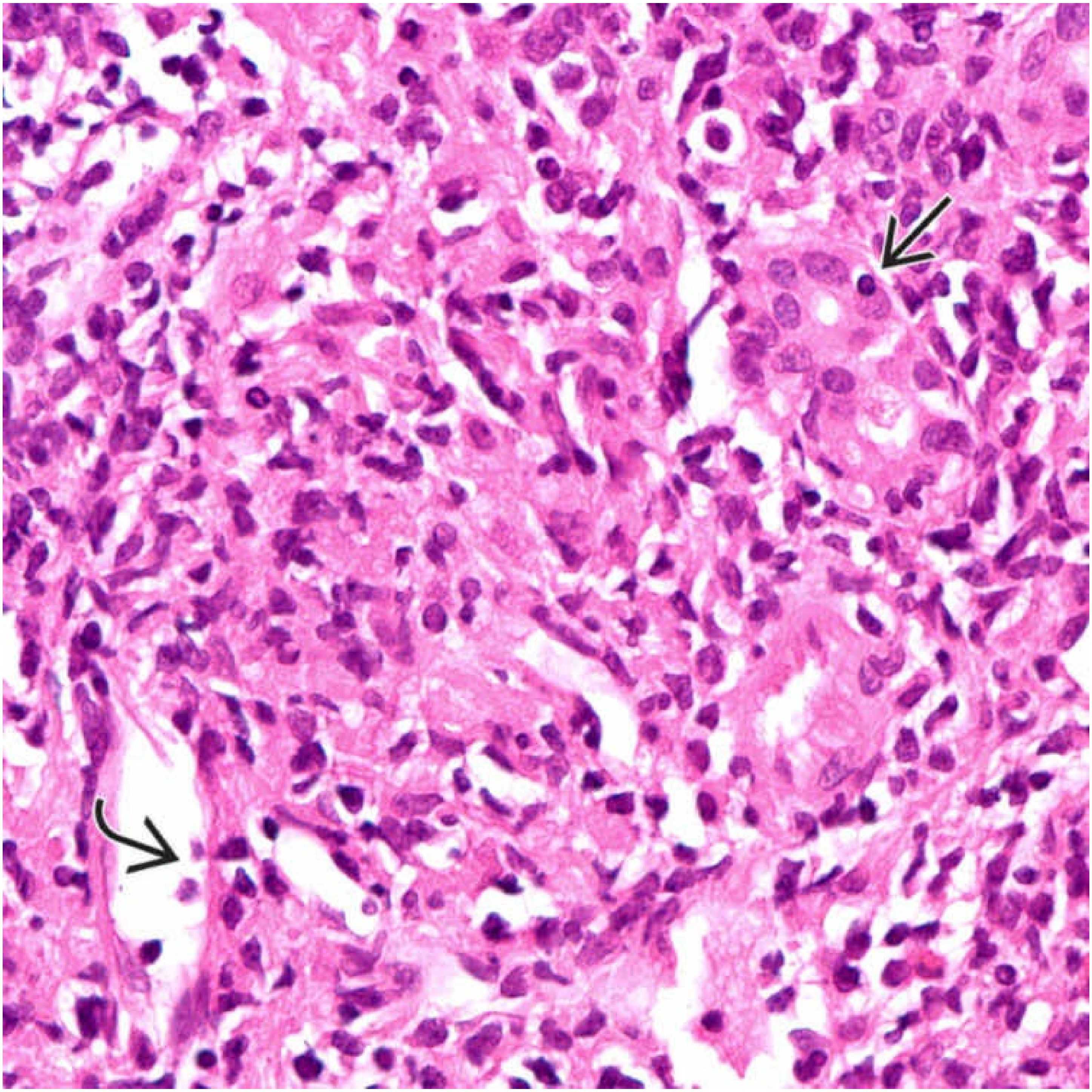
EBV-Associated Posttransplant Lymphoproliferative Disorder
This photomicrograph shows a case of EBV-associated classic Hodgkin lymphoma in a liver allograft. There are mixed portal infiltrates with scattered large cells, which are positive for CD15, CD30, fascin, and pax-5 (Hodgkin cells).



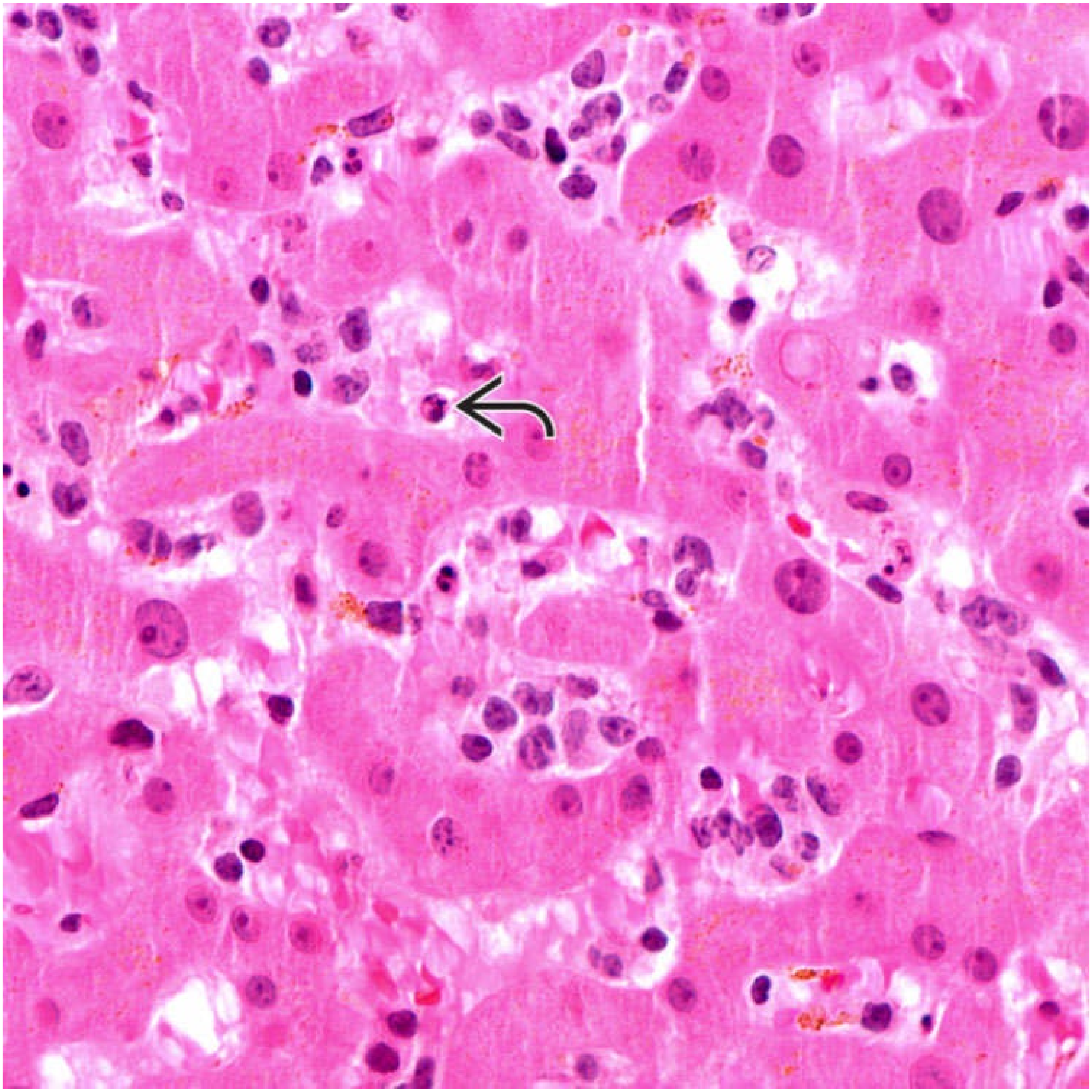
This biopsy from a case of EBV hepatitis is shows portal and lobular inflammation consisting predominantly of lymphocytes. Prominent sinusoidal lymphocytes can be appreciated even at this low power. There is also mild steatosis, unrelated to EBV infection.



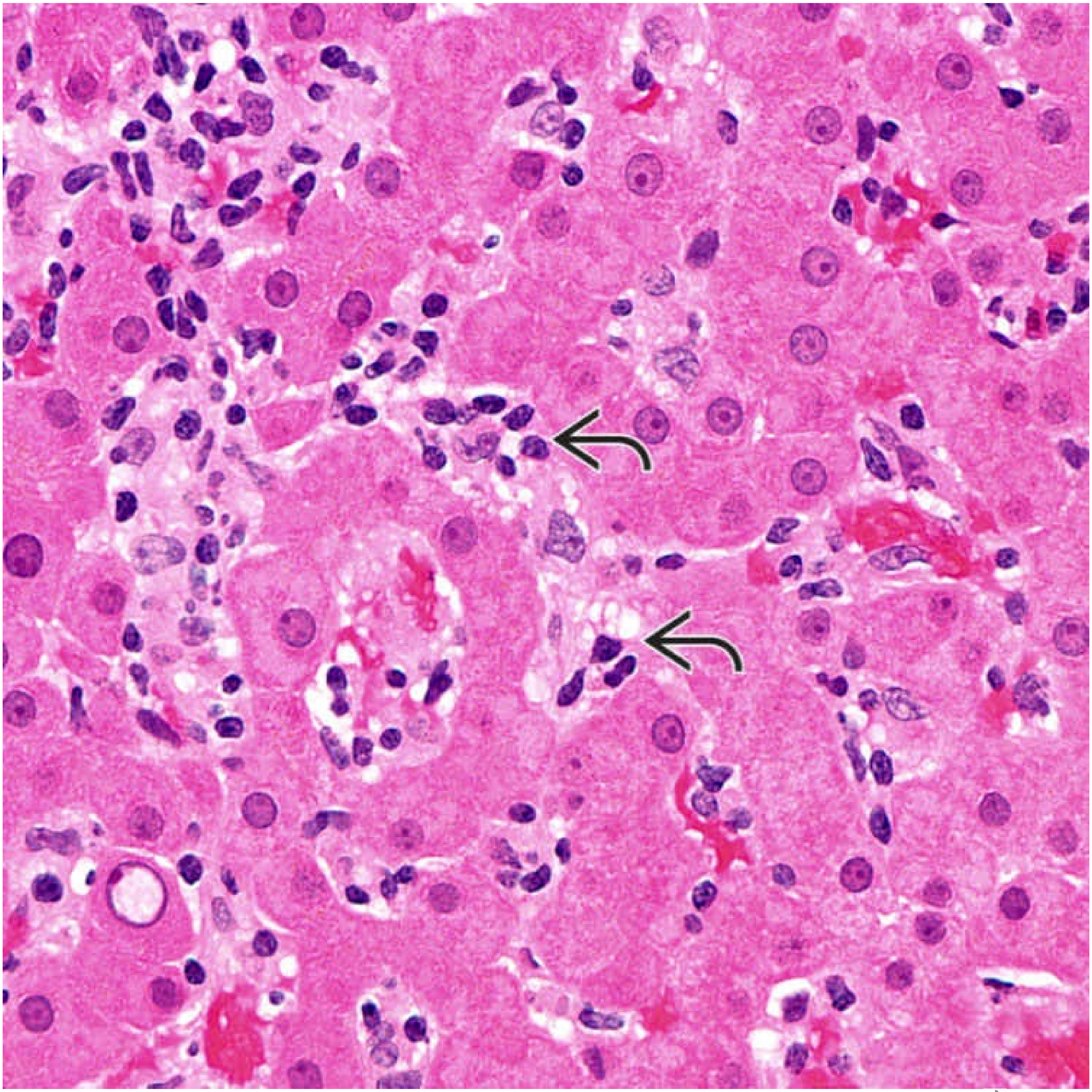
This case of EBV hepatitis shows portal ⇒ and lobular lymphocytic infiltrates. Note the Indian file or string of beads linear pattern of lymphocytes in the sinusoids.



EBV hepatitis causes predominantly lymphocytic infiltrates in the portal tracts. Note the presence of focal mild endophlebitis and mild bile duct damage, which may be confused with acute rejection in the transplant setting.



This case of hepatosplenic T-cell lymphoma shows monotonous, medium-sized lymphoid cells infiltrating the sinusoids and mimicking EBV hepatitis. However, note the presence of frequent mitotic figures in tumor cells. This rare type of lymphoma can also occur post transplantation.



This case of phenytoin-induced hepatitis also shows diffuse sinusoidal infiltration by lymphocytes, mimicking EBV hepatitis. Clinical history is essential to the correct diagnosis.

SELECTED REFERENCES

1. Dierickx, D, et al. Posttransplant lymphoproliferative disorders following liver transplantation: Where are we now? *World J Gastroenterol*. 2015; 21(39):11034–11043.
2. Khedmat, H, et al. Lymphoproliferative disorders in pediatric liver allograft recipients: a review of 212 cases. *Hematol Oncol Stem Cell Ther*. 2012; 5(2):84–90.
3. Suh, N, et al. Epstein-Barr virus hepatitis: diagnostic value of in situ hybridization, polymerase chain reaction, and immunohistochemistry on liver biopsy from immunocompetent patients. *Am J Surg Pathol*. 2007; 31(9):1403–1409.

Cytomegalovirus

KEY FACTS

Terminology

- At least 60% of adults in USA have serologic evidence of past infection
  - Most clinically significant infections are seen in setting of immunosuppression

Etiology/Pathogenesis

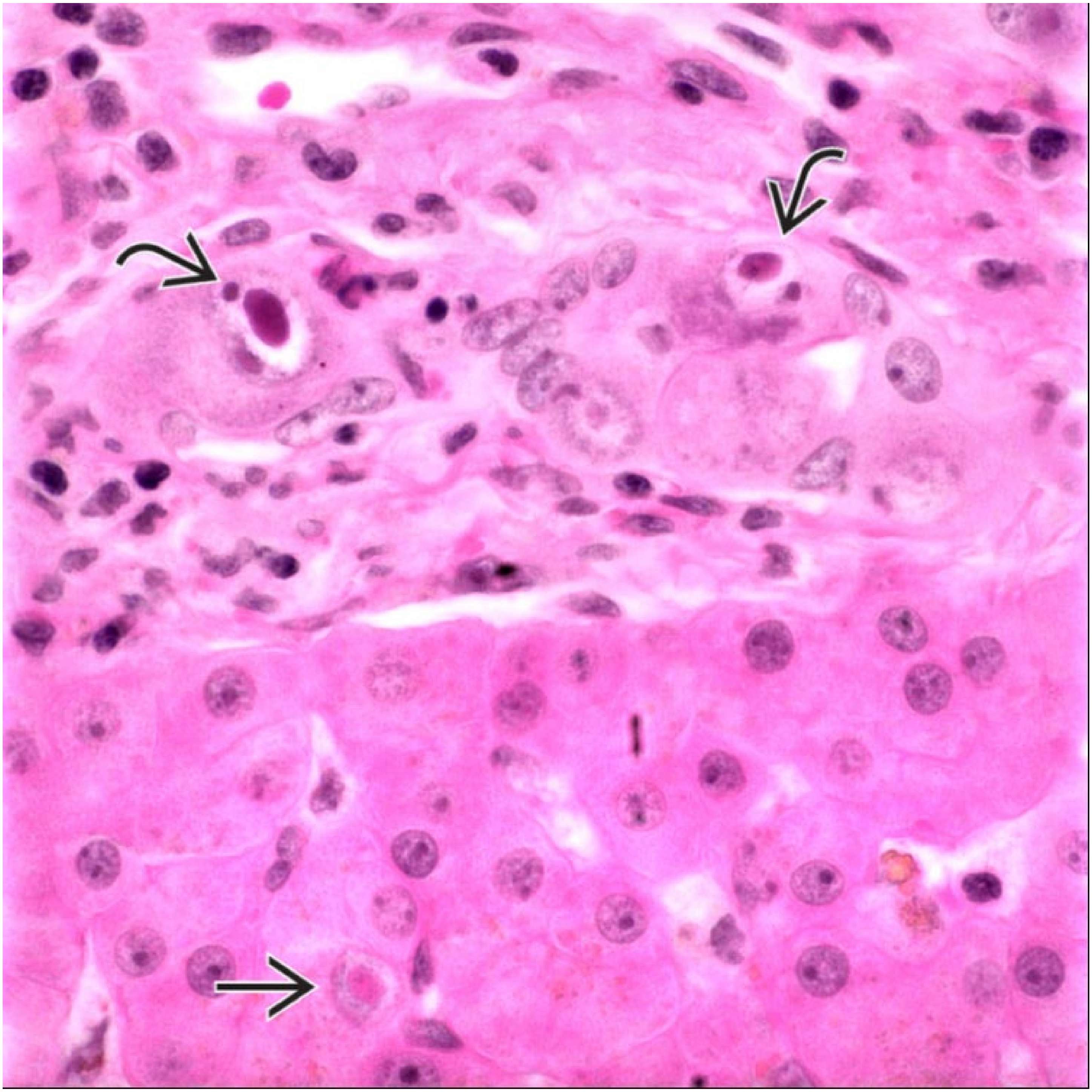
- Infection can be acquired before birth, at birth, or later in life
  - Following active infection, latent infection may persist for years

Clinical Issues

- Clinical (and histologic) presentation of CMV hepatitis depends on age and immune status of patient
  - Most infections in immunocompetent patients are clinically silent
  - Immunocompromised patients have highly variable presentation
  – Highest risk of infection in transplant patients is seronegative recipient/seropositive donor
- Congenital infection ranges from asymptomatic to severe
- Helpful laboratory tests include serologies and PCR from blood

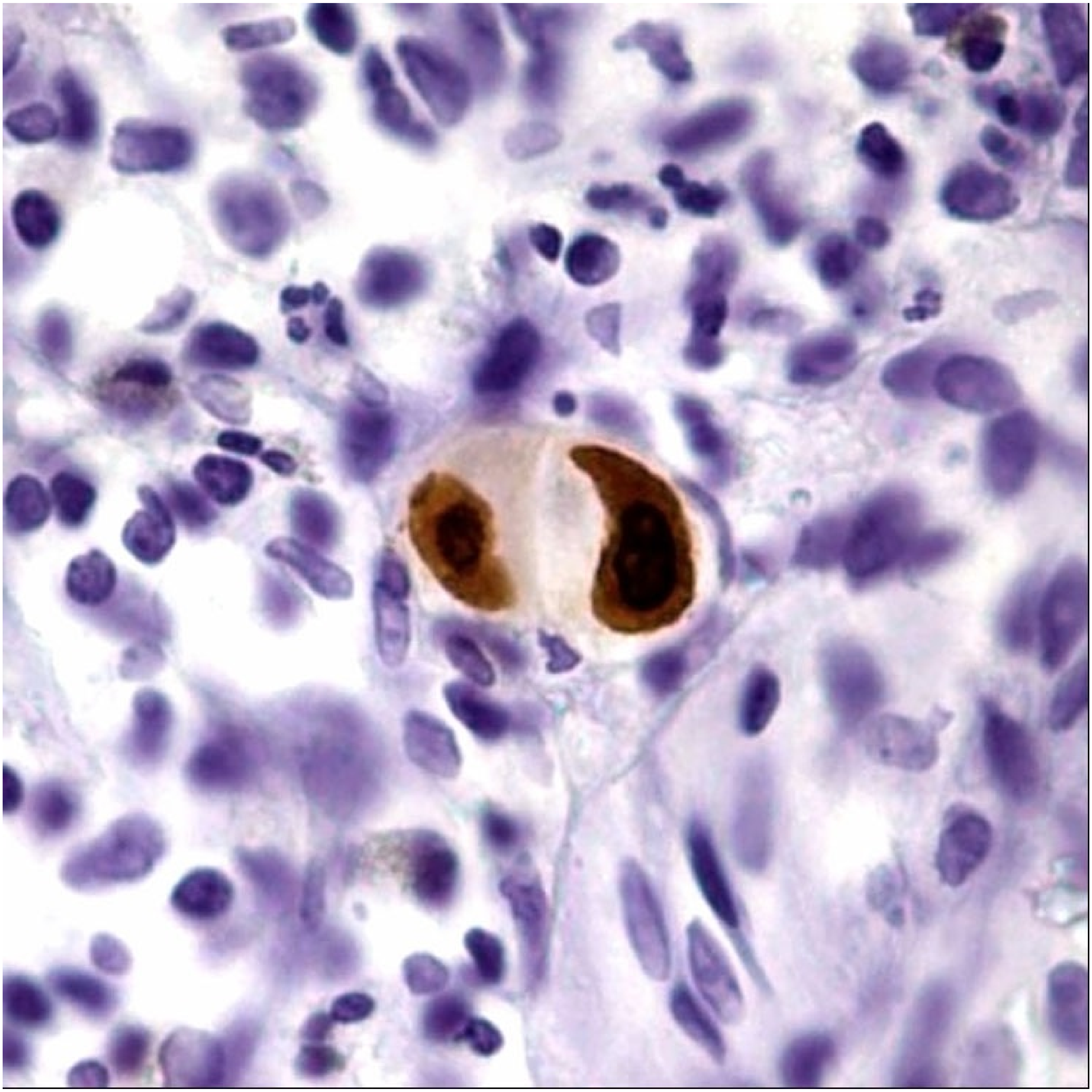
Microscopic

- Characteristic cytoplasmic and nuclear enlargement with intranuclear and intracytoplasmic inclusions
  - Inclusions can be seen within hepatocytes, biliary epithelium, endothelial cells, and Kupffer cells
  - Immunocompromised and neonatal patients have variably present portal and lobular inflammation
- Immunocompetent patients can have mononucleosis-like pattern with sinusoidal lymphocytic infiltrate and absence of viral inclusions

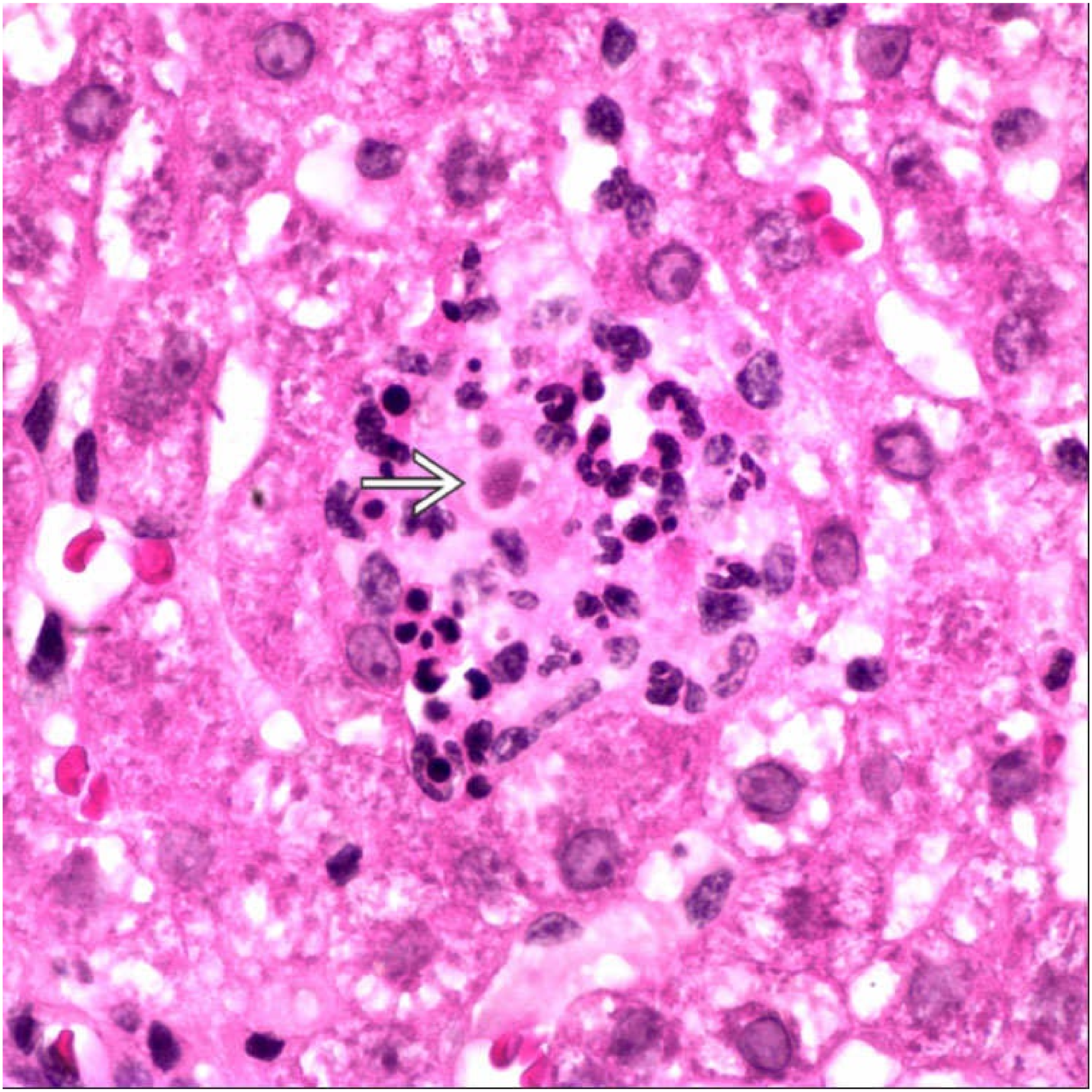


Cytomegalovirus Inclusions

Both biliary epithelium ↷ and hepatocytes → contain characteristic CMV inclusions. The nuclear inclusions have a halo around them that confers the characteristic owl's eye appearance.

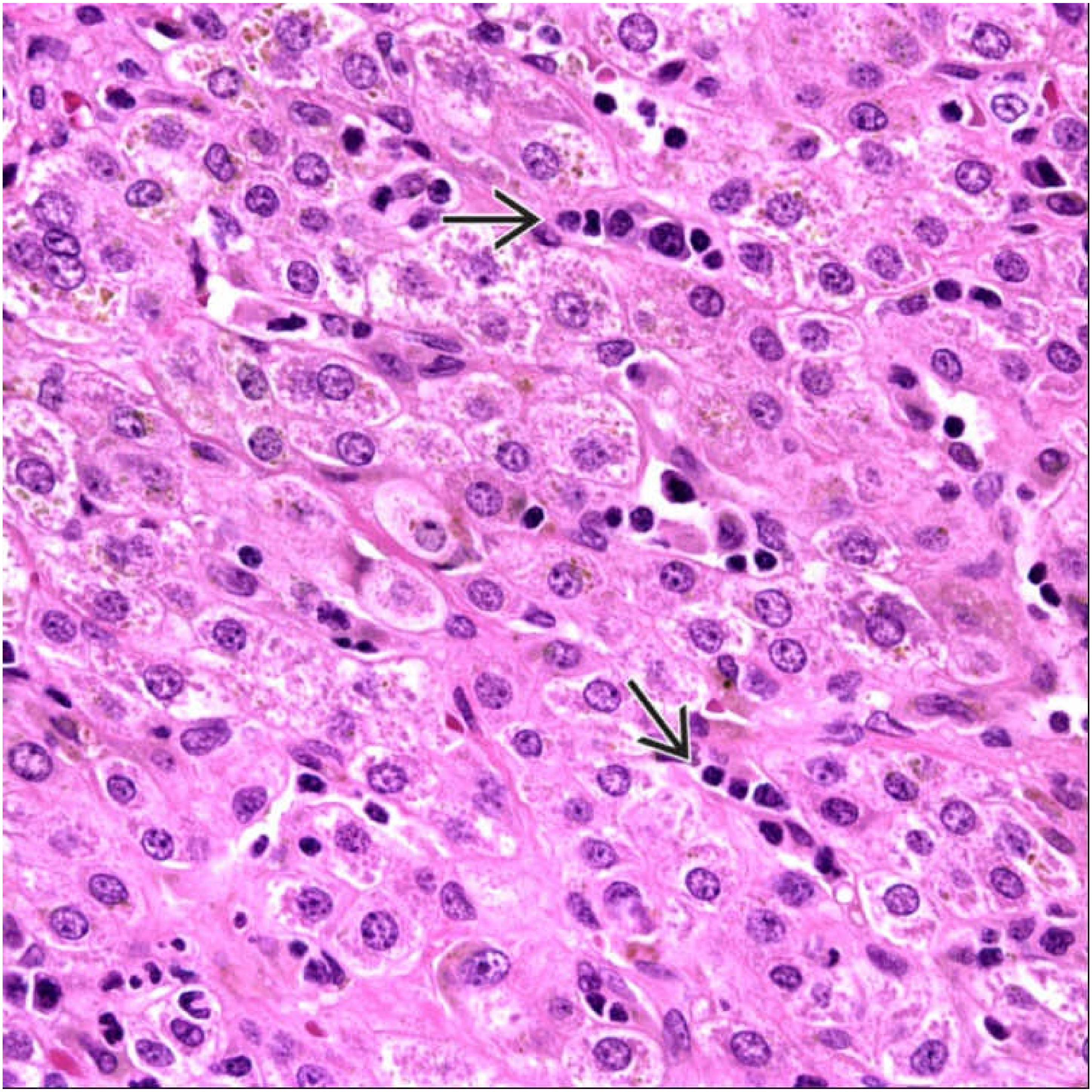


Cytomegalovirus Immunohistochemistry
CMV immunohistochemistry highlights 2 viral inclusions within endothelial cells in a small capillary.



Microabscess

Lobular neutrophilic microabscesses may be a histologic clue to hepatic CMV infection. An inclusion ⇒ is seen in the center of the microabscess in this liver transplant patient.



Lobular Lymphocytosis
Some cases of CMV feature a mononucleosis-like pattern similar to EBV infection in the liver, with a lobular lymphocytic infiltrate within the hepatic sinusoids in a string of beads configuration →.

TERMINOLOGY

Abbreviations

- Cytomegalovirus (CMV)

Synonyms

- HHV-5

Definitions

- Member of Herpesviridae family, capable of infecting many cell types
  - Identified in numerous body fluids (blood, semen, saliva)
- At least 60% of adults in USA have serologic evidence of past infection
  - Higher rates in developing countries and in HIV(+) patients
- Most clinically significant infections are seen in setting of immunosuppression
  - Organ transplantation, AIDS, congenital infection

ETIOLOGY/PATHOGENESIS

Infection

- Can be acquired before birth, at birth, or later in life
  - Following active infection, latent infection may persist for years
  - Reactivation typically occurs when normal immunity is lost or impaired
- Pathogenesis of CMV hepatitis is unclear
  - Direct viral damage &/or host inflammatory response may play roles in producing functional liver abnormalities

CLINICAL ISSUES

Presentation

- Most infections in immunocompetent patients are clinically silent
  - Rare immunocompetent patients manifest mononucleosis-like illness
- Immunocompromised patients have highly variable presentation
  - Fever, malaise, myalgias, arthralgias, nausea, abdominal pain
  - Allograft recipients' symptoms usually develop from 2 weeks to 4 months after transplantation
    - Highest risk of infection is seronegative recipient/seropositive donor
    - Reactivation of latent infection may also occur in immunocompromised patients
    - Associated with increased risk of rejection in transplant patients
- Congenital infection: Variable presentation ranging from asymptomatic to severe infection with jaundice, hepatosplenomegaly, encephalitis, chorioretinitis

Laboratory Tests

- PCR from blood
  - Used for diagnosis as well as monitoring in transplant patients
  - Does not correlate with organ-specific disease
- Serologies
  - Less useful in immunocompromised patients

Treatment

- Antiviral therapy (ganciclovir, valganciclovir) &/or reduce immunosuppression

- Prophylaxis and vigilant monitoring for infection in transplant patients

Prognosis

- Depends on host immune status
  - Resolve spontaneously in immunocompetent people
  - Mononucleosis-like pattern usually resolves within several weeks
  - Chronic liver disease very rare

MICROSCOPIC

Histologic Features

- Characteristic cytopathic effects of CMV
  - Cytoplasmic and nuclear enlargement (2-4x normal)
  - Inclusions within hepatocytes, biliary epithelium, endothelial cells, and Kupffer cells
  - – Intranuclear: Large glassy round to oval inclusions with surrounding halo (owl's eye)
  - – Intracytoplasmic: Basophilic or amphophilic granules
- Positive on immunohistochemical stain for CMV
- Patterns of inflammation
  - Mononucleosis-like pattern
    - Prominent mononuclear infiltrate within portal tracts and sinusoids (string of beads pattern)
    - Viral inclusions typically absent
    - Occasional granulomas
- Immunosuppressed patients
  - CMV inclusions along with mild lobular hepatitis, hepatocellular necrosis, patchy mononuclear portal inflammation, &/or neutrophilic microabscesses
  - Inflammation may be absent in severely immunocompromised patients
- Congenital infections
  - Resemble those of immunosuppressed patients (including presence of viral cytopathic effects)
  - Some have neonatal hepatitis-like pattern (cholestasis, hepatocyte necrosis) or features that simulate biliary atresia (bile ductular proliferation and portal fibrosis)
  - Extramedullary hematopoiesis is common finding

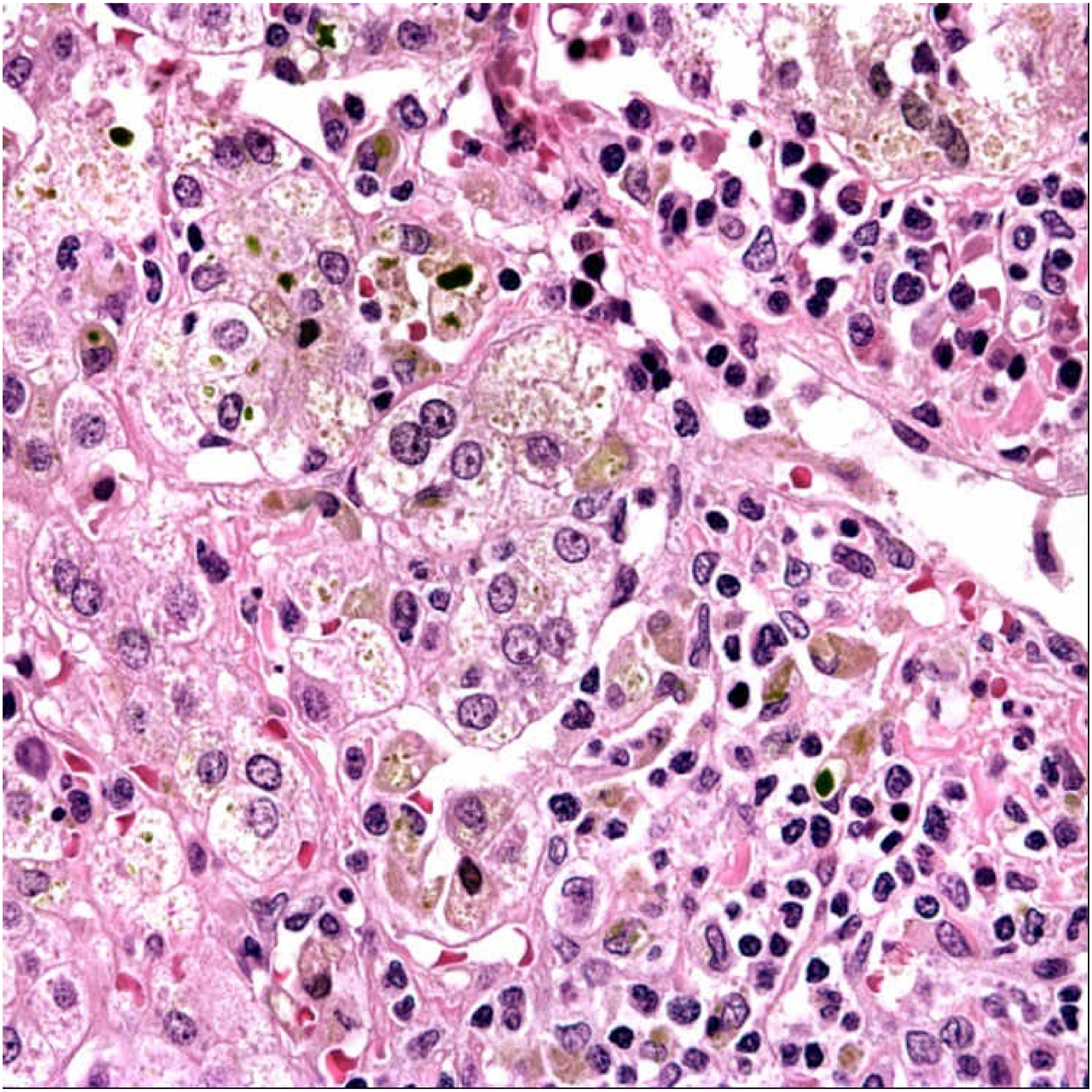
DIFFERENTIAL DIAGNOSIS

Epstein-Barr-Associated Hepatitis

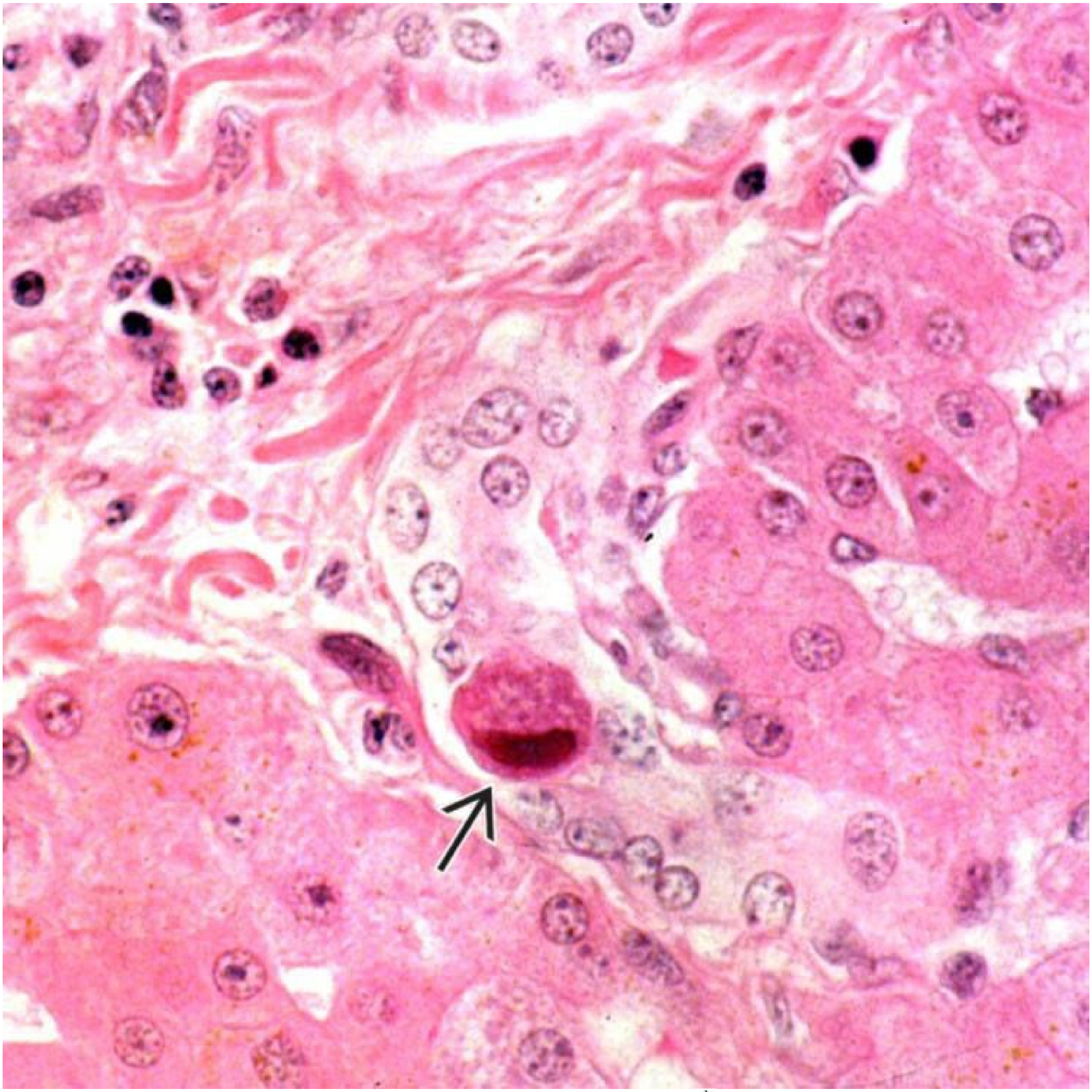
- EBV(+) serologies; lack of CMV inclusions

Other Viral Infections

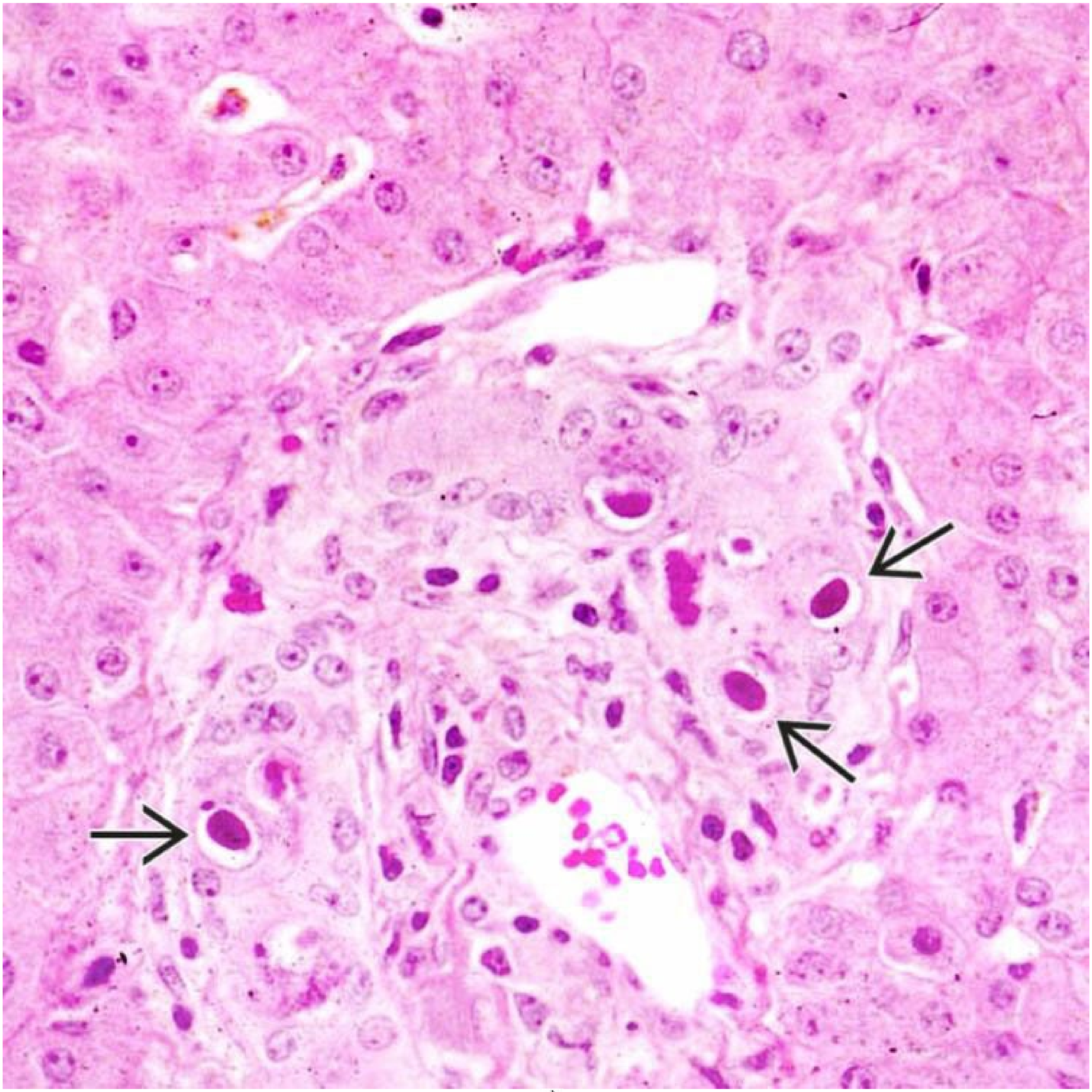
- i.e., HSV, adenovirus, varicella-zoster virus
- Immunohistochemical stains, serologies, clinical context are helpful



Congenital CMV infections can show a neonatal, hepatitis-like pattern with cholestasis. This case illustrates hepatocellular and canalicular cholestasis with a mononuclear parenchymal infiltrate.



A CMV inclusion is present within a portal tract in biliary epithelium →. Note how much bigger the cell harboring the inclusion is than the neighboring epithelial cells, hence the name cytomegalovirus.



This portal tract contains numerous CMV inclusions →. There is very little associated inflammation in this immunosuppressed transplant patient.

SELECTED REFERENCES

1. Marcelin, JR, et al. Cytomegalovirus infection in liver transplant recipients: updates on clinical management. *World J Gastroenterol*. 2014; 20(31):10658–10667.
2. Pedersen, M, et al. Infections after orthotopic liver transplantation. *J Clin Exp Hepatol*. 2014; 4(4):347–360.
3. Varani, S, et al. Cytomegalovirus as a hepatotropic virus. *Clin Lab*. 2002; 48(1-2):39–44.
4. Griffiths, PD. Cytomegalovirus and the liver. *Semin Liver Dis*. 1984; 4(4):307–313.

Herpes Simplex Virus

KEY FACTS

Etiology/Pathogenesis

- Hepatitis is result of disseminated infection and can occur with both herpes simplex virus 1 and 2 (HSV1 and HSV2)

Clinical Issues

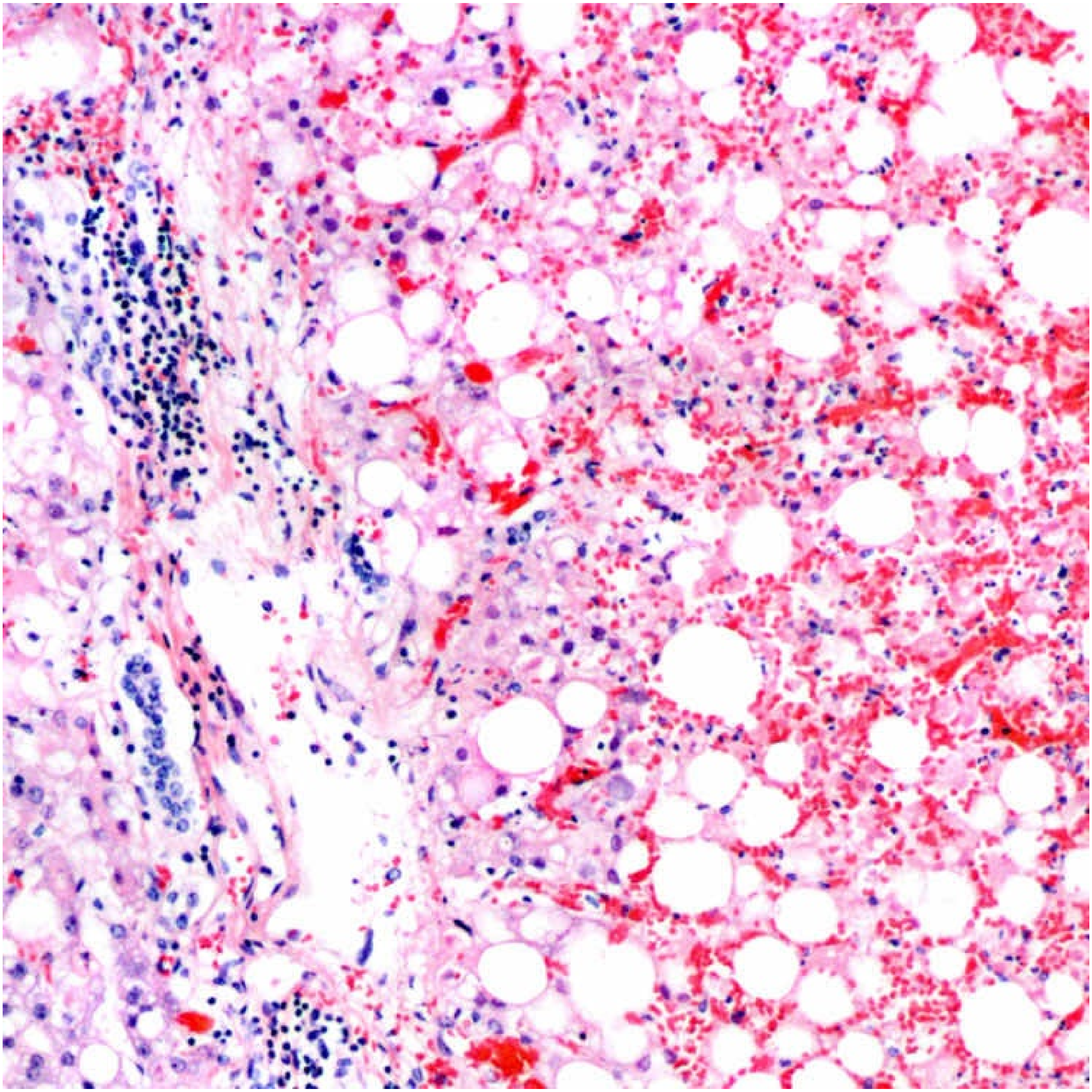
- Anicteric hepatitis with marked elevation of transaminases
- Mucocutaneous or genital manifestations in 30-50% of cases
- Early treatment is crucial as disease can follow rapidly progressive course
- Antiviral therapy with acyclovir
- Risk factors: Immunosuppression, neonates, pregnancy

Microscopic

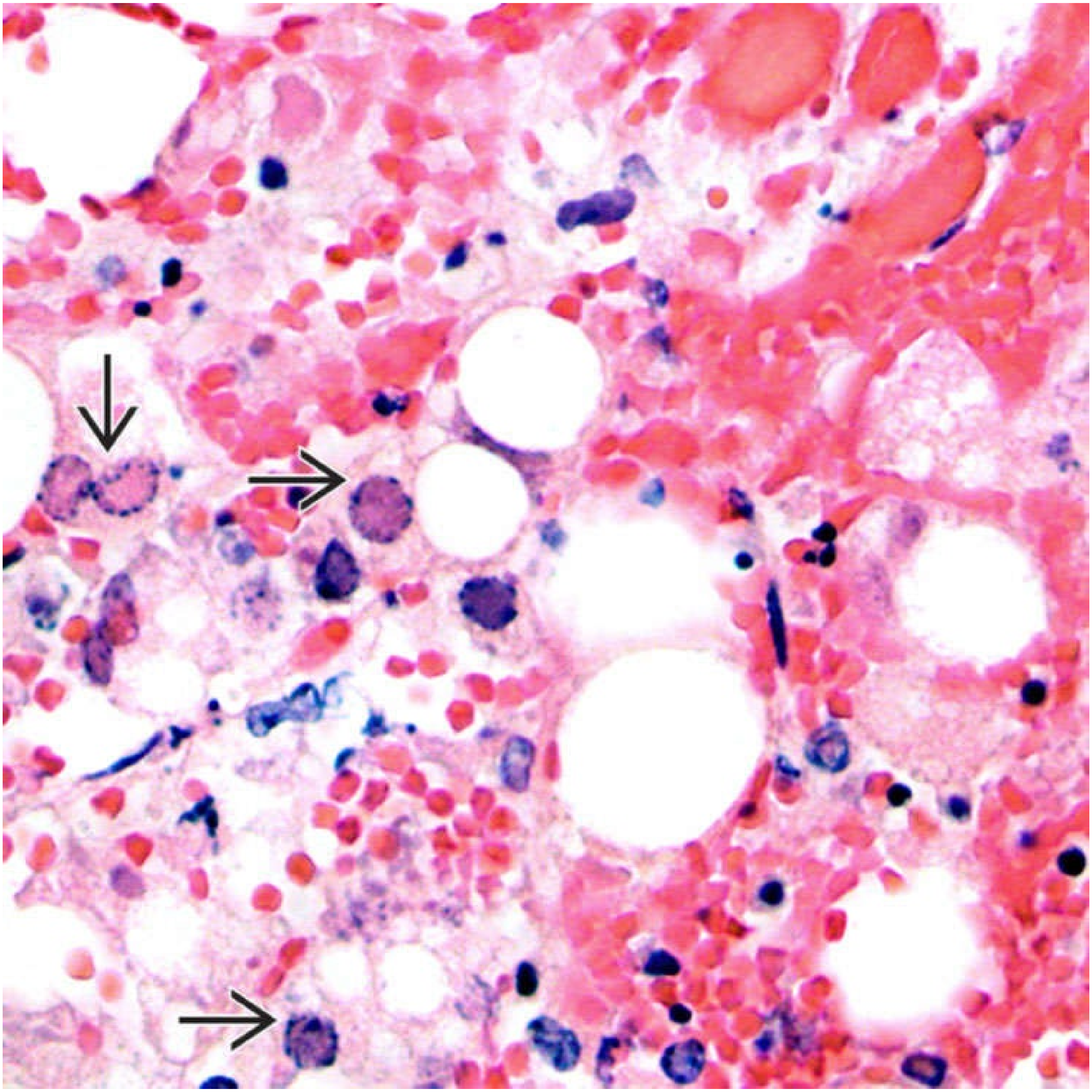
- Extensive nonzonal coagulative necrosis with negligible inflammation
  - Viral inclusions in hepatocyte nuclei at interface of necrotic and viable areas
  - Characterized by ground-glass or smudged nuclei with margination of chromatin
- Multinucleated cells with nuclear molding are less common compared with mucocutaneous HSV infections
- Immunohistochemistry with antibodies directed against HSV1/HSV2 confirm diagnosis

Top Differential Diagnoses

- Acetaminophen toxicity
- Toxin-induced liver injury
- Adenovirus hepatitis
- Wilson disease
- Acute vascular injury

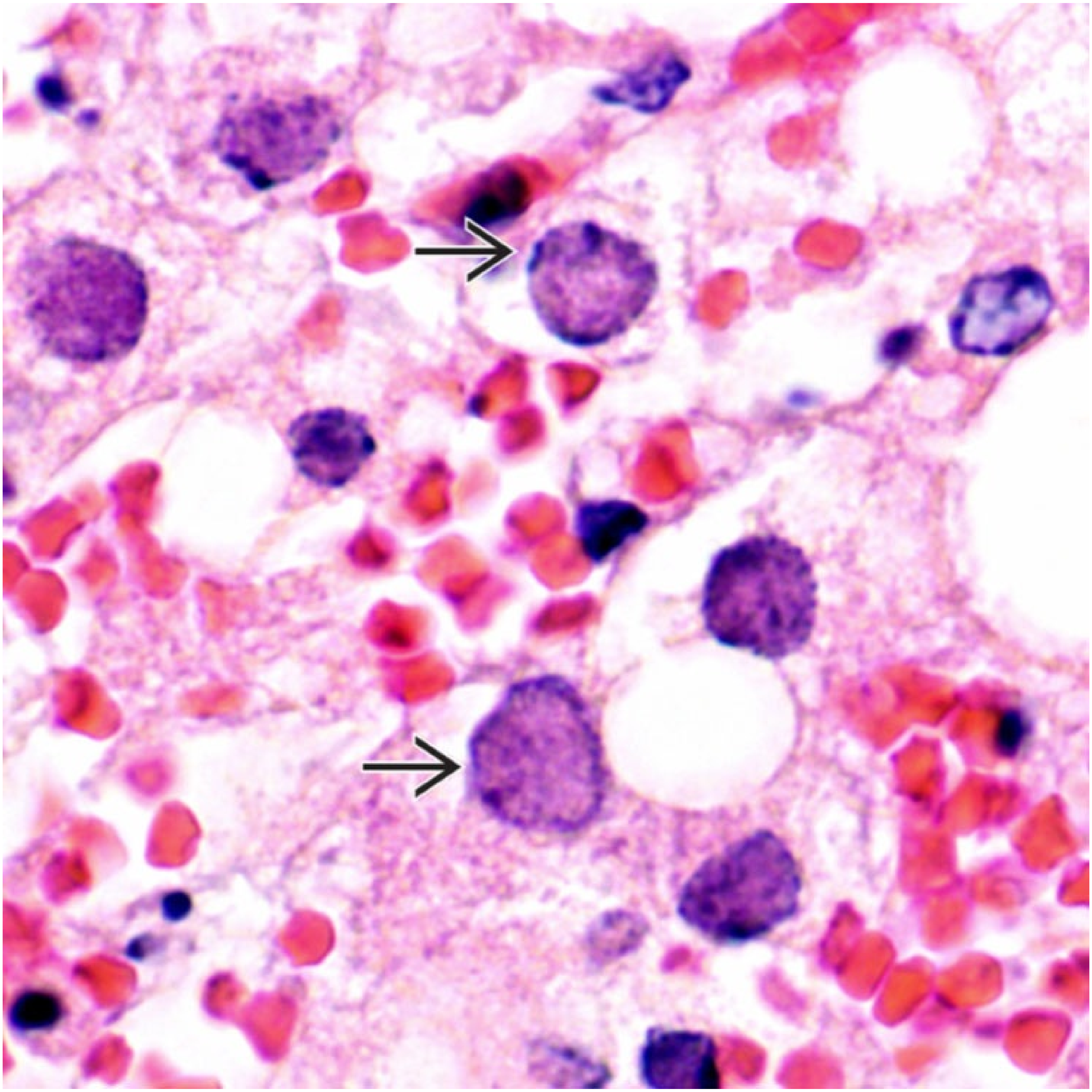


Minimal Inflammation
H&E shows extensive hemorrhagic necrosis with negligible portal and lobular inflammation.



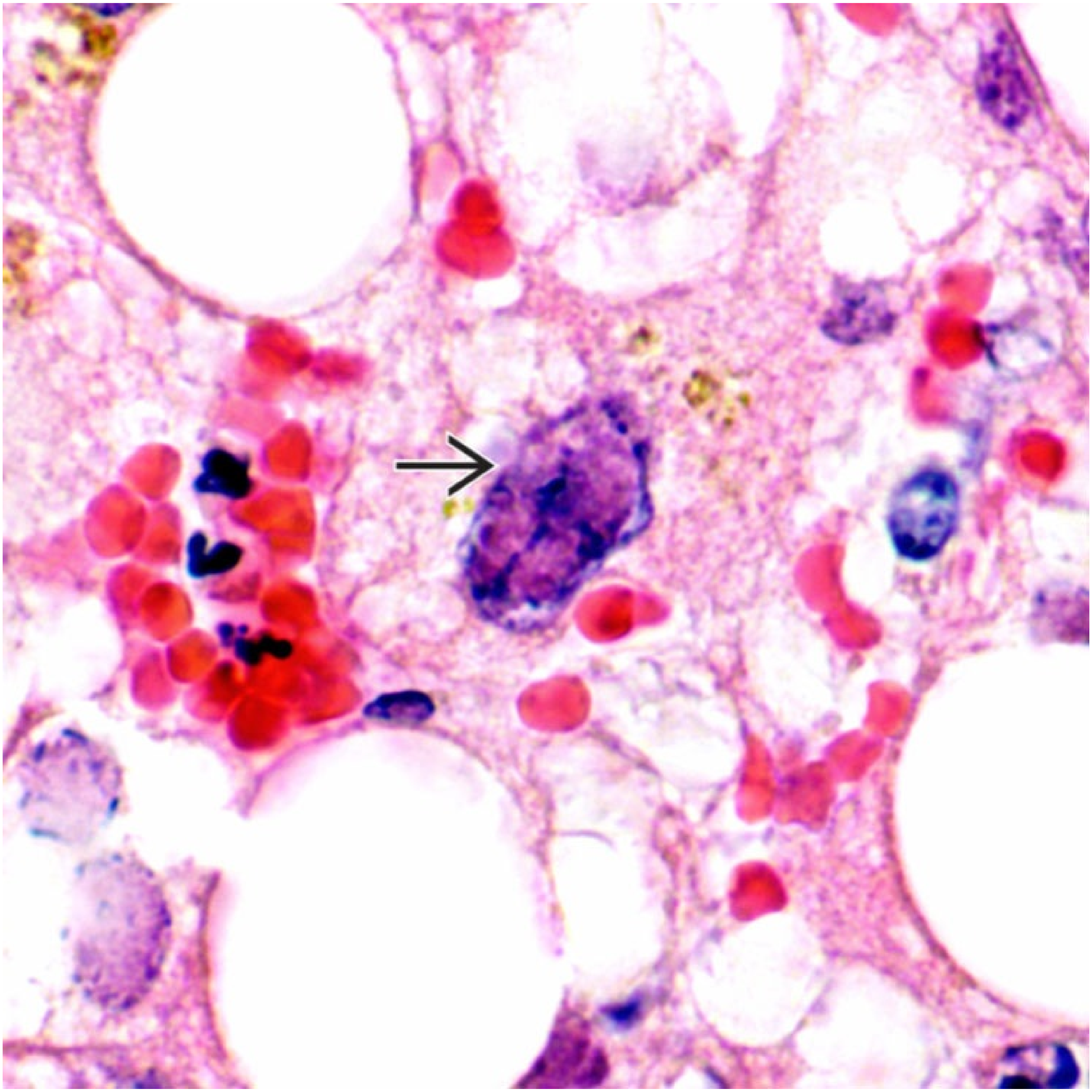
Nuclear Inclusions

H&E shows herpes simplex virus (HSV) inclusions at the interface of necrotic and viable areas. In most cells, the inclusions appear as eosinophilic ground-glass areas in the nucleus with margination of nuclear chromatin →.



Nuclear Inclusions

H&E shows viral inclusions → with smudged hepatocyte nuclei and margination of nuclear chromatin. The inclusions are typically located at the edge of necrotic zones. A prominent owl-eye like appearance typical of CMV inclusions is not present in most HSV inclusions.



Multinucleated Cell
H&E shows a multinucleated cell → with nuclear molding. These cells are commonly observed in herpetic mucosal lesions but are uncommon in HSV hepatitis.

TERMINOLOGY

Abbreviations

- Herpes simplex virus (HSV) hepatitis

ETIOLOGY/PATHOGENESIS

Infectious Agents

- Hepatitis is result of disseminated infection and can occur with both HSV1 and HSV2
- Dissemination may occur due to immunosuppression, large initial inoculum, enhanced virulence at reactivation, or hepatovirulence of certain strains

CLINICAL ISSUES

Epidemiology

- Incidence
  - Risk factors
    - Immunosuppression
    - Neonates
    - 3rd trimester of pregnancy
- Fulminant infections rare in immunocompetent individuals

Presentation

- Nonspecific flu-like symptoms
  - Fever, headache, abdominal/muscle pain
- Oropharyngeal or genital manifestations in 30-50% of cases
- Acute decompensation 3-21 days after nonspecific symptoms
  - Anicteric
  - No hepatomegaly
  - Marked elevation of transaminases (AST > ALT)
  - Leukopenia, thrombocytopenia
  - Encephalitis, renal failure, and disseminated intravascular coagulation can occur
- Neonatal HSV typically presents 5-7 days after birth and mimics bacterial sepsis (poor feeding, lethargy, fever)

Laboratory Tests

- Viral culture: mucocutaneous lesions, urine, stool, blood
- PCR for viral DNA using plasma, body fluids, tissue

Treatment

- Antiviral drugs: Acyclovir and adenine arabinoside
- Early treatment is crucial as disease can follow rapidly progressive course

Prognosis

- High mortality (80-90%) in untreated cases
- Survival is better in pregnant patients

MICROSCOPIC

Histologic Features

- Extensive nonzonal coagulative hemorrhagic necrosis
  - Inflammatory response is inconspicuous
  - Viral inclusions at interface of necrotic and viable areas
    - Ground-glass or smudged nuclei with margination of chromatin
    - Eosinophilic intranuclear inclusions surrounded by halo (Cowdry type A) can be present
    - Multinucleated cells with nuclear molding are less common compared with mucocutaneous HSV infections
- Immunohistochemistry with antibodies directed against HSV1/HSV2 should be used

Predominant Pattern/Injury Type

- Necrosis

Predominant Cell/Compartment Type

- Hepatocyte

DIFFERENTIAL DIAGNOSIS

Acetaminophen Toxicity

- Necrosis, often perivenular, without significant inflammation
- History of drug intake, elevated blood levels of drug, and absence of viral inclusions

Toxin-Induced Liver Injury

- Mushroom poisoning, cocaine, herbal medications, carbon tetrachloride
- Necrosis without significant inflammation
- History of exposure and absence of viral inclusions

Adenovirus Hepatitis

- Usually affects immunosuppressed patients
- Immunohistochemistry necessary to distinguish from HSV; inclusions very similar

Wilson Disease

- Rarely presents as fulminant hepatitis with necrosis and no significant inflammation
- Elevated hepatic copper, urinary copper, low ceruloplasmin
- No viral inclusions

Acute Vascular Injury

- Acute ischemia (circulatory shock) or venous outflow obstruction (Budd-Chiari syndrome)
- Hemorrhagic necrosis around central vein
- Sinusoidal dilatation in venous outflow obstruction
- No viral inclusions

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Look for inclusions at interface between necrotic zones and viable parenchyma

SELECTED REFERENCES

1. Czartoski, T, et al. Fulminant, acyclovir-resistant, herpes simplex virus type 2 hepatitis in an immunocompetent woman. *J Clin Microbiol*. 2006; 44(4):1584–1586.
2. Verma, A, et al. Neonatal herpes simplex virus infection presenting as acute liver failure: prevalent role of herpes simplex virus type I. *J Pediatr Gastroenterol Nutr*. 2006; 42(3):282–286.
3. Sharma, S, et al. Herpes simplex hepatitis in adults: a search for muco-cutaneous clues. *J Clin Gastroenterol*. 2004; 38(8):697–704.
4. Peters, DJ, et al. Herpes simplex-induced fulminant hepatitis in adults: a call for empiric therapy. *Dig Dis Sci*. 2000; 45(12):2399–2404.

Adenovirus

KEY FACTS

Etiology/Pathogenesis

- Nonenveloped, double-stranded DNA viruses that include 57 serotypes known to infect humans
- Serotypes 1, 2, and 5 are most common hepatic isolates
- Incubation time of 2-14 days for new infection

Clinical Issues

- Mild, self-limited illnesses in immunocompetent individuals
- Fulminant hepatitis occurring in setting of severe immunosuppression, usually fatal with > 50% mortality rate
- No virus-specific therapy; successful treatment with cidofovir, ribavirin, or serum immunoglobulin containing high titers of neutralizing antibody to adenovirus has been reported

Imaging

- Hypodense lesions in liver on CT

Macroscopic

- Hepatomegaly with mottled foci of necrosis

Microscopic

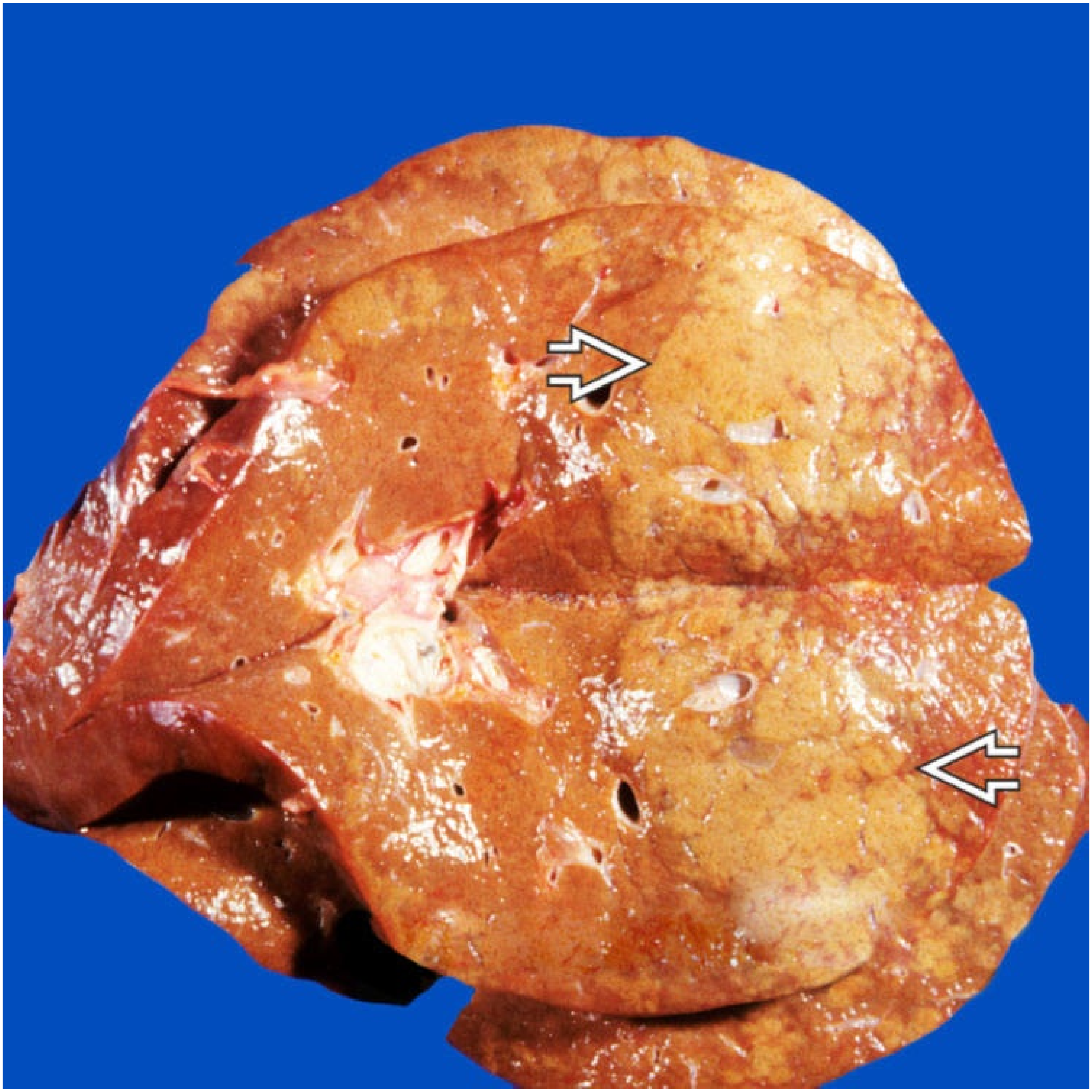
- Random small or large foci of coagulative necrosis of hepatocytes
- No or minimal inflammatory response around necrotic foci
- Intranuclear viral inclusions with characteristic smudgy nuclear appearance and chromatin margination in infected hepatocytes commonly seen at periphery of necrotic foci

Ancillary Tests

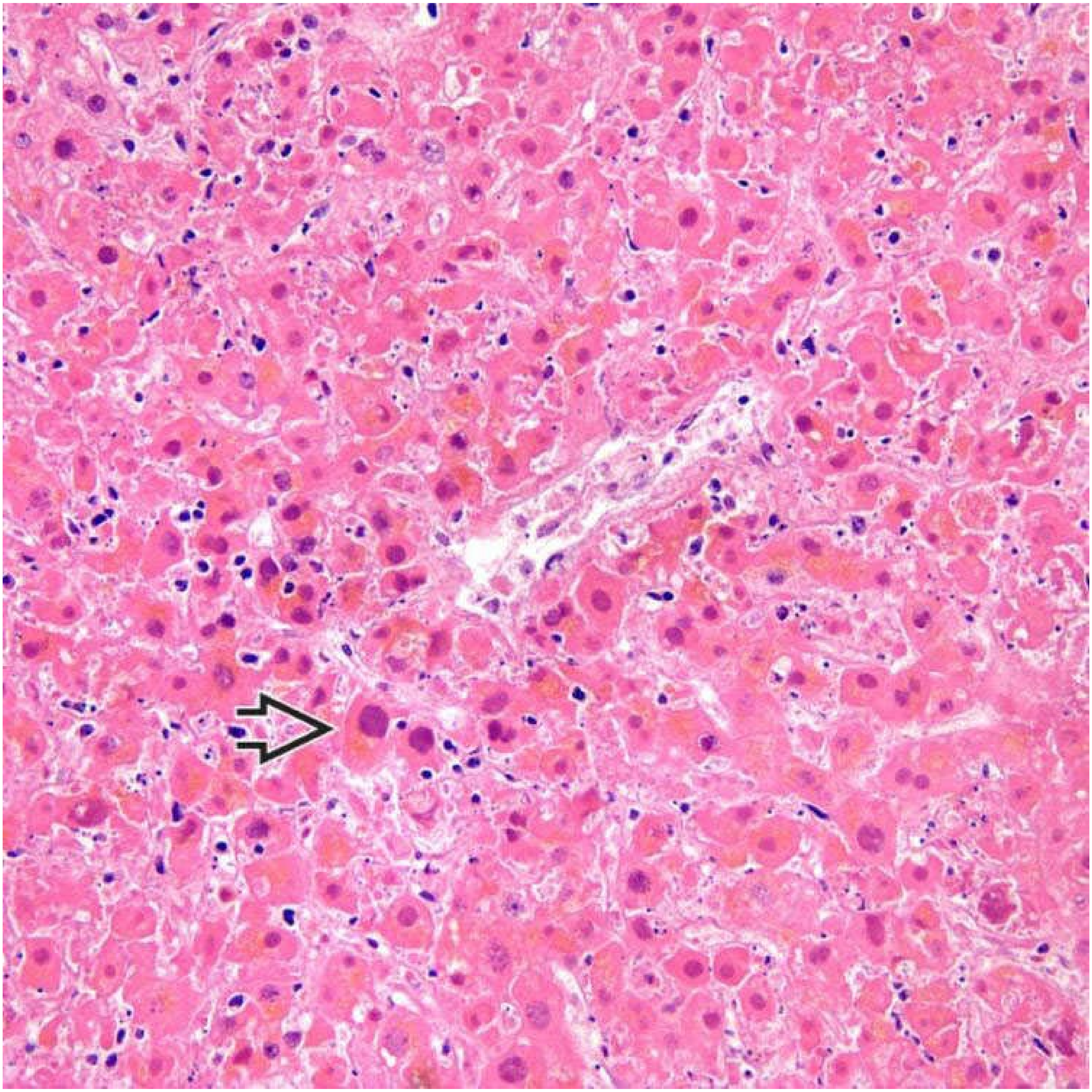
- Immunohistochemistry
- Polymerase chain reaction

Top Differential Diagnoses

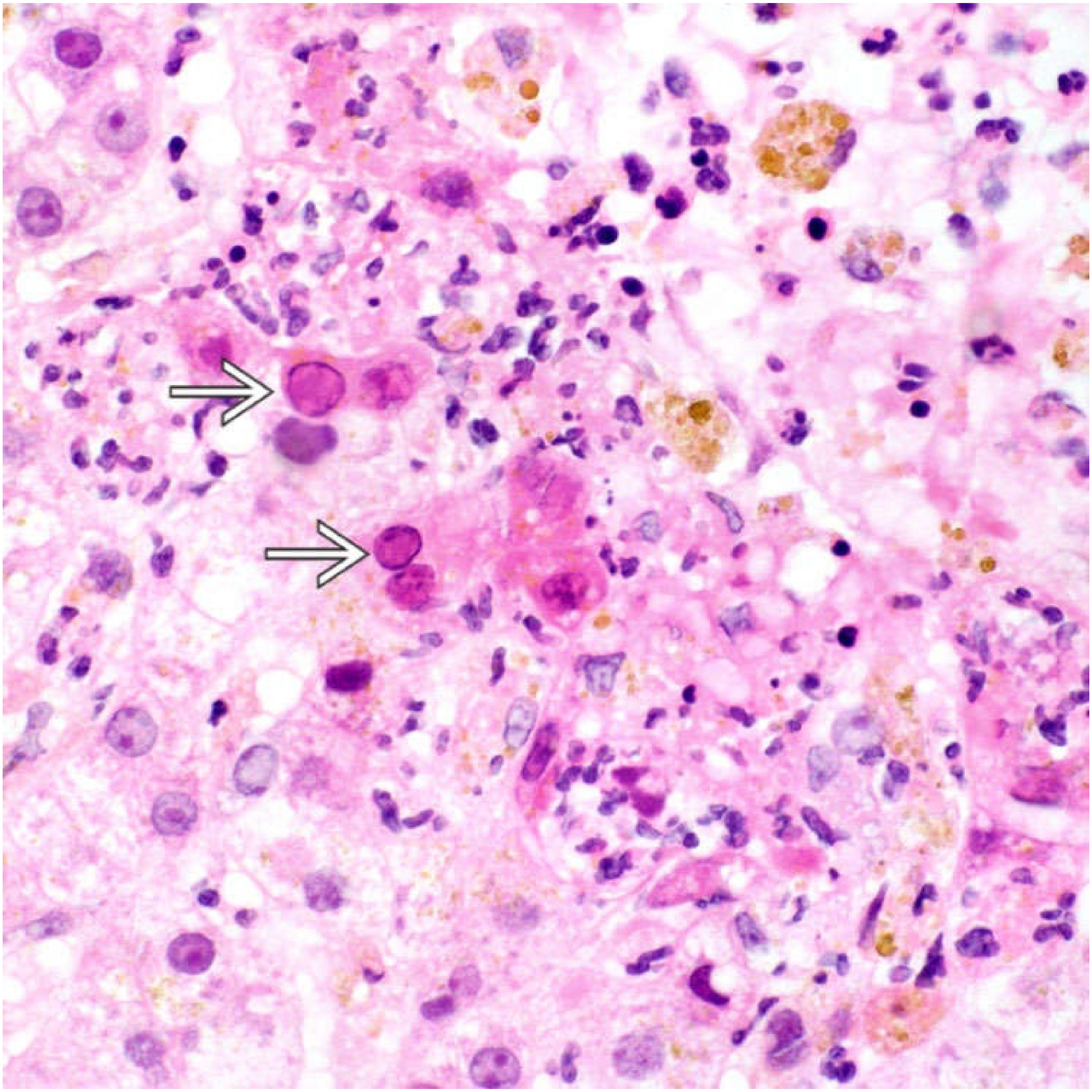
- Herpes simplex virus hepatitis
  - Infected hepatocytes may be slightly enlarged and multinucleated
  - May show hemorrhagic appearance in areas of necrosis
- Varicella-zoster virus hepatitis
- CMV hepatitis



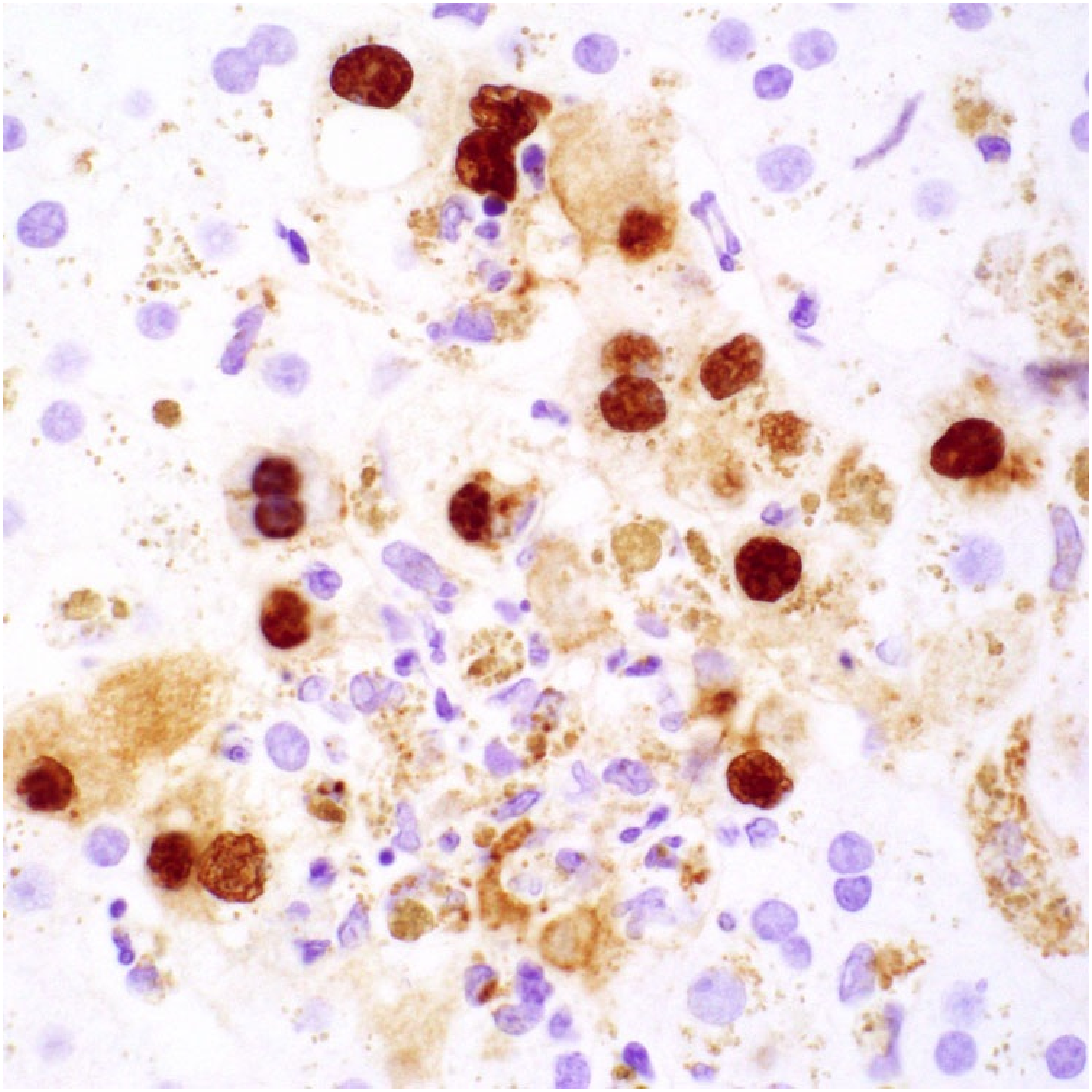
Gross Appearance
This liver specimen from an autopsy case shows large, irregular, variably sized, yellow-tan foci of necrosis ⇨ .



Necrosis With Minimal Inflammation
Large zones of necrosis with minimal inflammation, as seen here, are typical of adenovirus infection.
Dark, smudgy nuclear inclusions (“smudge cells”) are visible even at low power ➩ .



Smudge Cells
Hyperchromatic, smudgy nuclei, or “smudge cells” with chromatin margination ⇨ are characteristic of adenovirus infection. They are seen here within hepatocytes at the periphery of a necrotic focus. Note that the necrotic hepatocytes are largely dropped out in this case, accompanied by mild neutrophilic infiltrates.



Infected Hepatocytes
Immunohistochemical stain for adenovirus highlights infected hepatocytes with intense nuclear, and some cytoplasmic, reactivity.

TERMINOLOGY

Definitions

• Hepatitis caused by adenoviruses

ETIOLOGY/PATHOGENESIS

Infectious Agents

- Nonenveloped, double-stranded DNA viruses that include 57 serotypes known to infect humans
- Serotypes 1, 2, and 5 are most common hepatic isolates
- Primary infection or reactivation of latent infection
- Spread by aerosolized droplets, water, fomites, and donor organs as well as fecal-oral, ocular, and nosocomial routes
- Incubation time of 2-14 days for new infection

CLINICAL ISSUES

Presentation

- Mild, self-limited illnesses in immunocompetent individuals
  - Respiratory infection, keratoconjunctivitis, hemorrhagic cystitis, and gastroenteritis
- Severe diseases in immunocompromised patients
  - Hepatitis, pancreatitis, pneumonia, nephritis, encephalitis, or disseminated disease
- Fulminant hepatitis typically occurs in immunocompromised or transplant patients
  - High fever, jaundice
  - Marked elevation of serum transaminase levels

Laboratory Tests

- Detection of viral DNA by polymerase chain reaction
- Direct viral antigen detection
- Viral isolation by culture
- Serology

Treatment

- No virus-specific therapy
  - Successful treatment with cidofovir, ribavirin, or serum immunoglobulin containing high titers of neutralizing antibody to adenovirus has been reported
- Supportive care
- Reduction of immunosuppression

Prognosis

- Fulminant hepatitis is usually fatal with > 50% mortality rate

IMAGING

CT Findings

- Hypodense lesions in liver

MACROSCOPIC

General Features

- Hepatomegaly with mottled foci of necrosis

MICROSCOPIC

Histologic Features

- Random, variably sized foci of coagulative necrosis of hepatocytes
    - Minimal or no inflammatory response around necrotic foci
- Mild nonspecific lobular and portal inflammatory cell infiltrates consisting of lymphocytes, neutrophils, and eosinophils may be present
- Small, poorly formed granulomas and microabscesses may be seen
- Intranuclear viral inclusions with characteristic smudgy nuclear appearance and chromatin margination in infected hepatocytes
    - Commonly seen at periphery of necrotic foci
    - Infected hepatocytes do not exhibit cytomegaly or multinucleation
- Rarely viral inclusions noted in biliary epithelium, causing necrotizing cholangitis and bile duct loss

ANCILLARY TESTS

Immunohistochemistry

- Monoclonal antiadenovirus (blend) antibodies stain for infected cells

DIFFERENTIAL DIAGNOSIS

Herpes Simplex Virus Hepatitis

- Infected hepatocytes may be slightly enlarged and multinucleated
- May show hemorrhagic appearance in areas of necrosis
- Immunohistochemical stain is helpful

Varicella-Zoster Virus Hepatitis

- Histologically indistinguishable from herpes simplex virus hepatitis
- Presence of typical skin lesions
- Immunohistochemical stain and polymerase chain reaction are helpful

Cytomegalovirus Hepatitis

- Large eosinophilic nuclear viral inclusions typically surrounded by clear halo
- Presence of cytoplasmic viral inclusions

- Typically lack large foci of coagulative necrosis
- Microabscesses may be present
- Immunohistochemical stain is helpful

Drug-Induced Hepatitis

- May show more pronounced cholestasis &/or steatosis
- Lack of characteristic viral inclusions

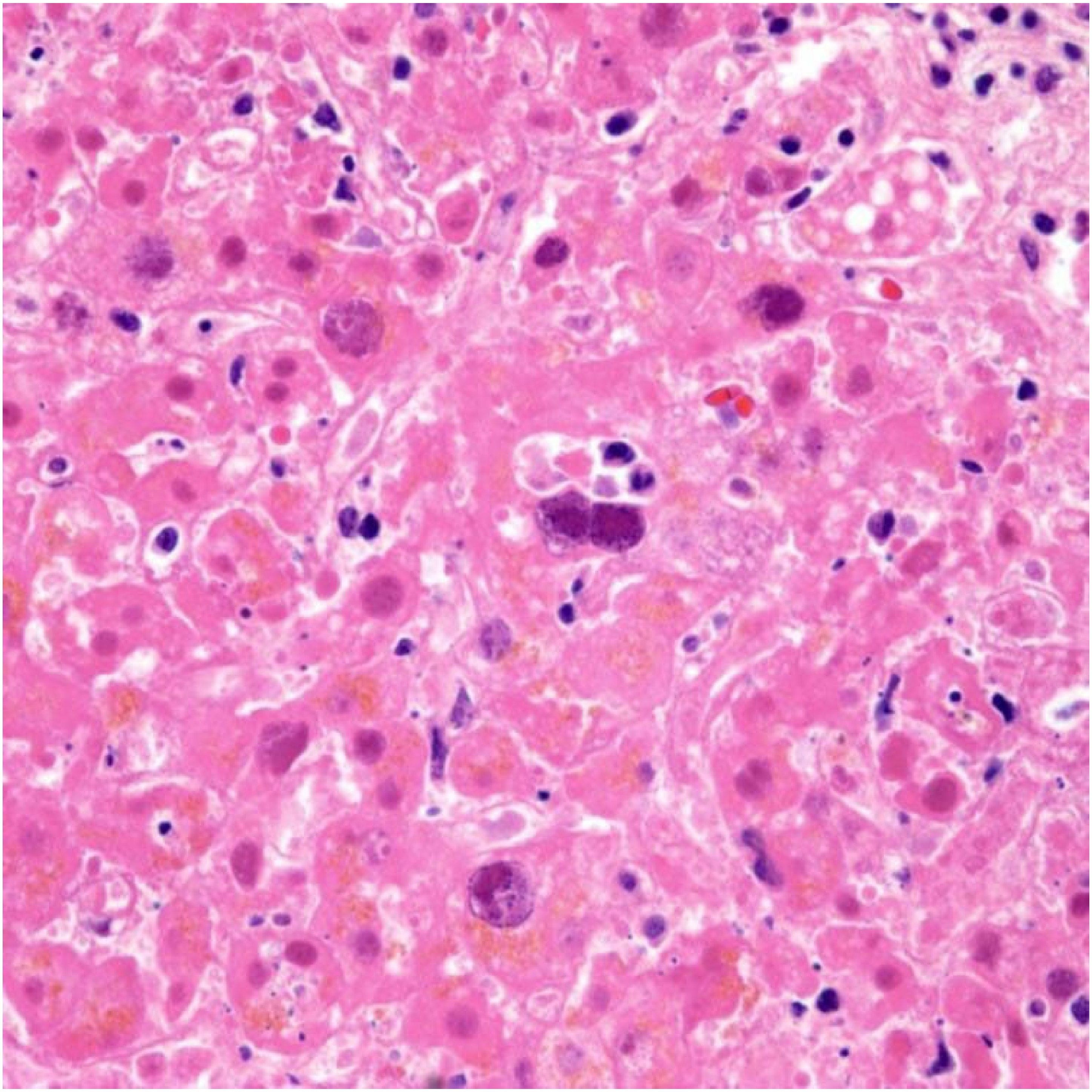
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

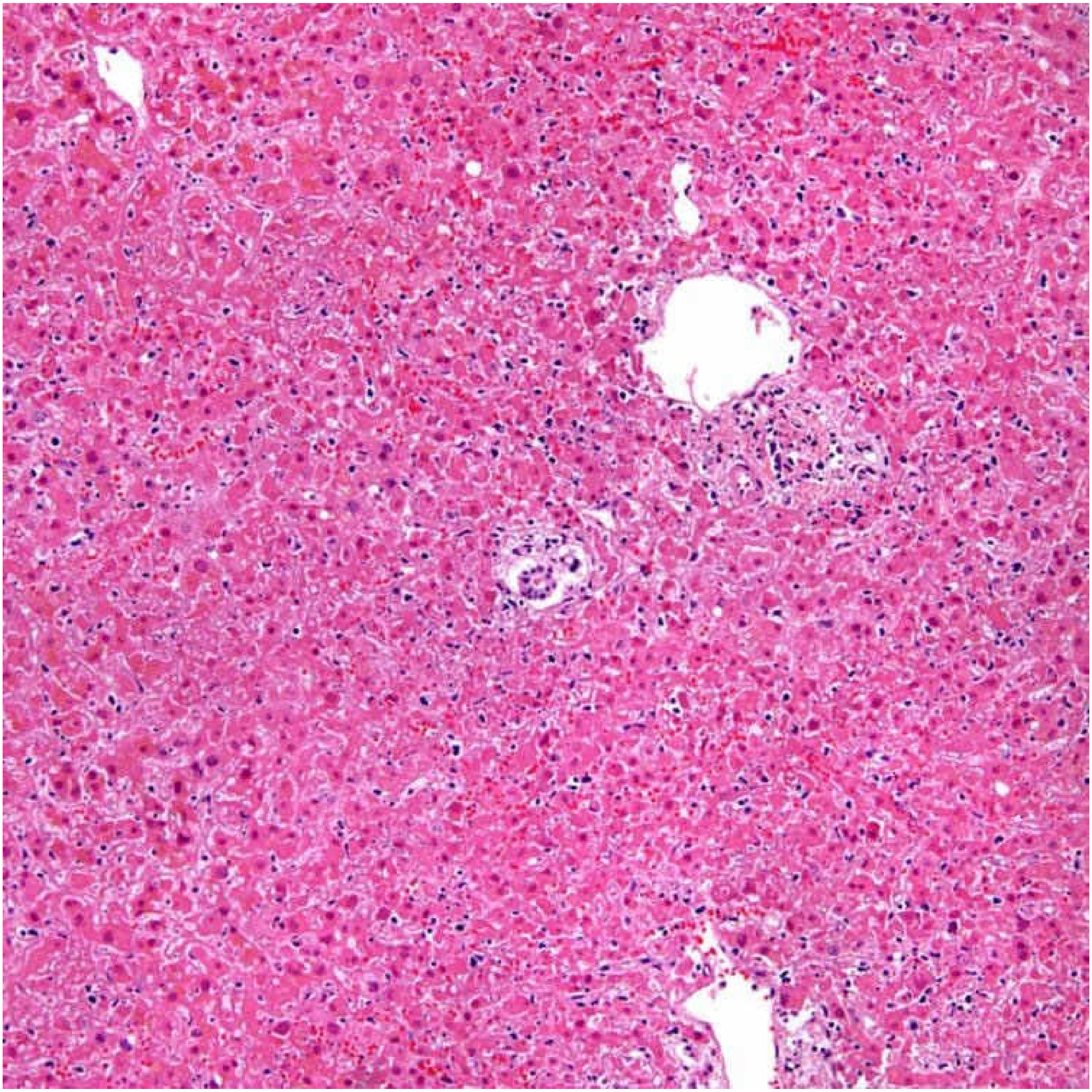
- Jaundice and hepatic failure in setting of severe immunosuppression

Pathologic Interpretation Pearls

- Foci of coagulative necrosis
- Characteristic nuclear viral inclusions



Hyperchromatic nuclei with smudgy chromatin are characteristic of cells with adenovirus nuclear inclusions. These are also known as “smudge cells.”



Extensive necrosis with minimal inflammation is characteristic of adenovirus infection in the liver. Rare intact portal tracts are seen.

SELECTED REFERENCES

1. Ronan, BA, et al. Fulminant hepatitis due to human adenovirus. *Infection*. 2014; 42(1):105–111.
2. Engelmann, G, et al. Adenovirus infection and treatment with cidofovir in children after liver transplantation. *Pediatr Transplant*. 2009; 13(4):421–428.
3. Echavarría, M. Adenoviruses in immunocompromised hosts. *Clin Microbiol Rev*. 2008; 21(4):704–715.
4. Wang, WH, et al. Fulminant adenovirus hepatitis following bone marrow transplantation. A case report and brief review of the literature. *Arch Pathol Lab Med*. 2003; 127(5):e246–e248.

Pyogenic Abscess

KEY FACTS

Terminology

- Localized accumulation of pus with surrounding inflammation and fibrosis, secondary to infection
  - Occurs via portal vein, arterial system, or bile ducts

Etiology/Pathogenesis

- Bacterial pathogens most common in Western countries
  - *Klebsiella pneumoniae* is now most common pathogen, followed by *Escherichia coli*
  - Anaerobes are isolated in up to 25% of cases
  - Significant number are cryptogenic

Clinical Issues

- Diabetes is major risk factor
  - Other associated conditions include intraabdominal infections, biliary disease, malignancy, cirrhosis
- Presentation includes fever, chills, RUQ pain
  - Elevated WBC count, ESR, CRP, bilirubin, alkaline phosphatase, transaminases
- Percutaneous drainage and antibiotics are mainstay of therapy
- Major complication is spread of infection
- Mortality ~ 15% overall

Imaging

- Ultrasound &/or CT mainstay of diagnosis

Macroscopic

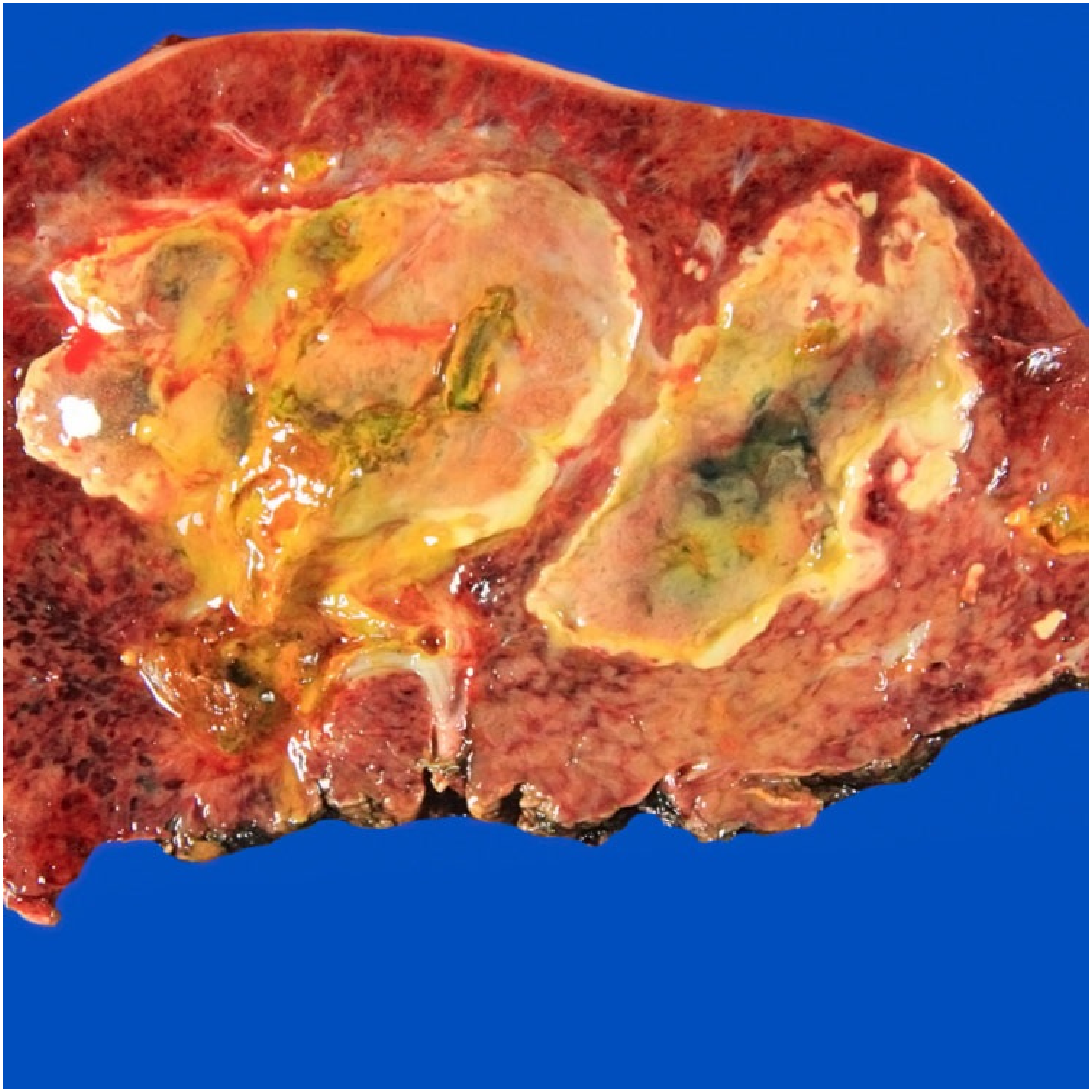
- Most abscesses are solitary; multiple abscesses occur in 25-45% of cases
  - Right lobe most frequent site

Microscopic

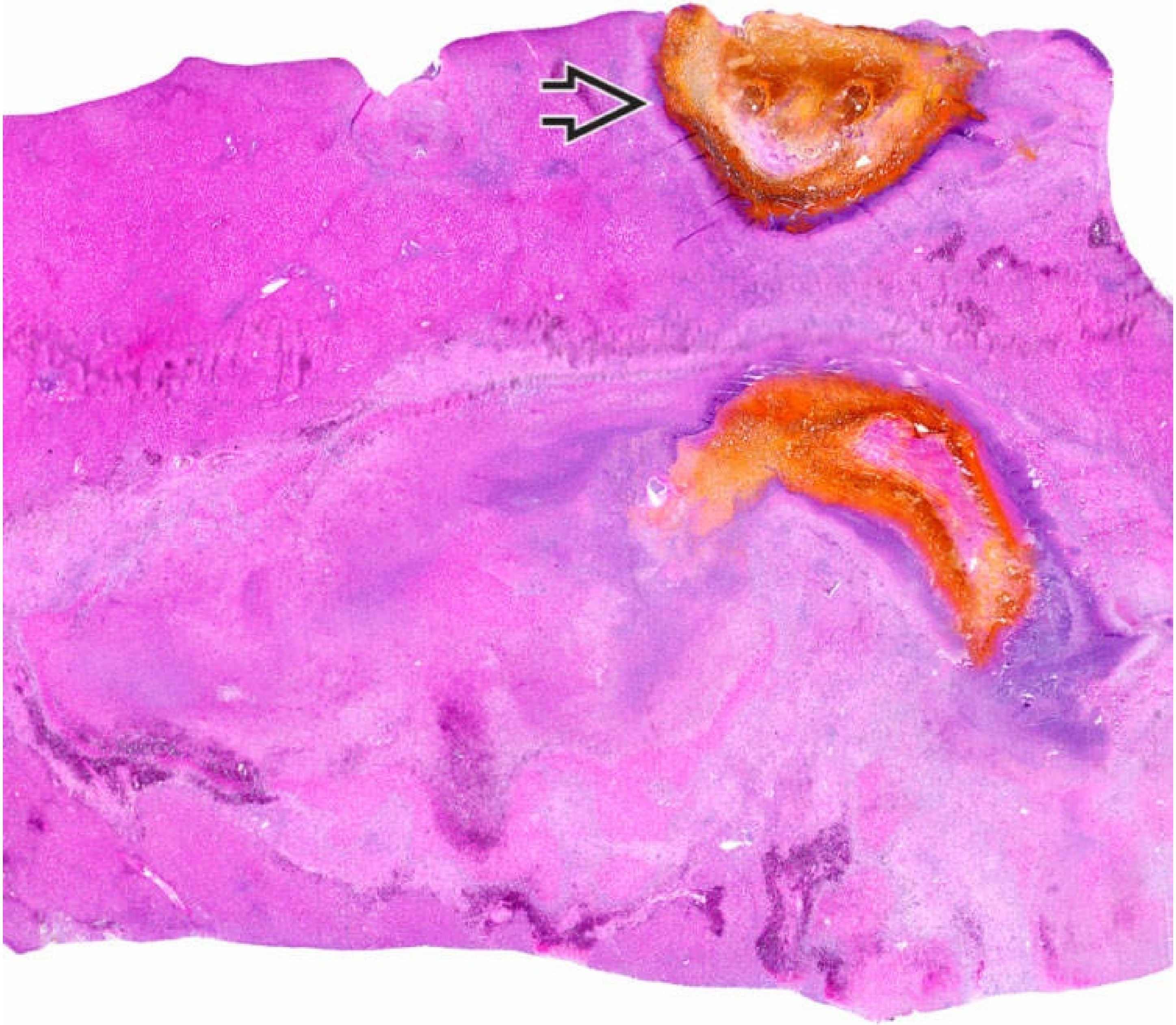
- Abundant neutrophils, fibrin, and bile with associated fibrosis

Diagnostic Checklist

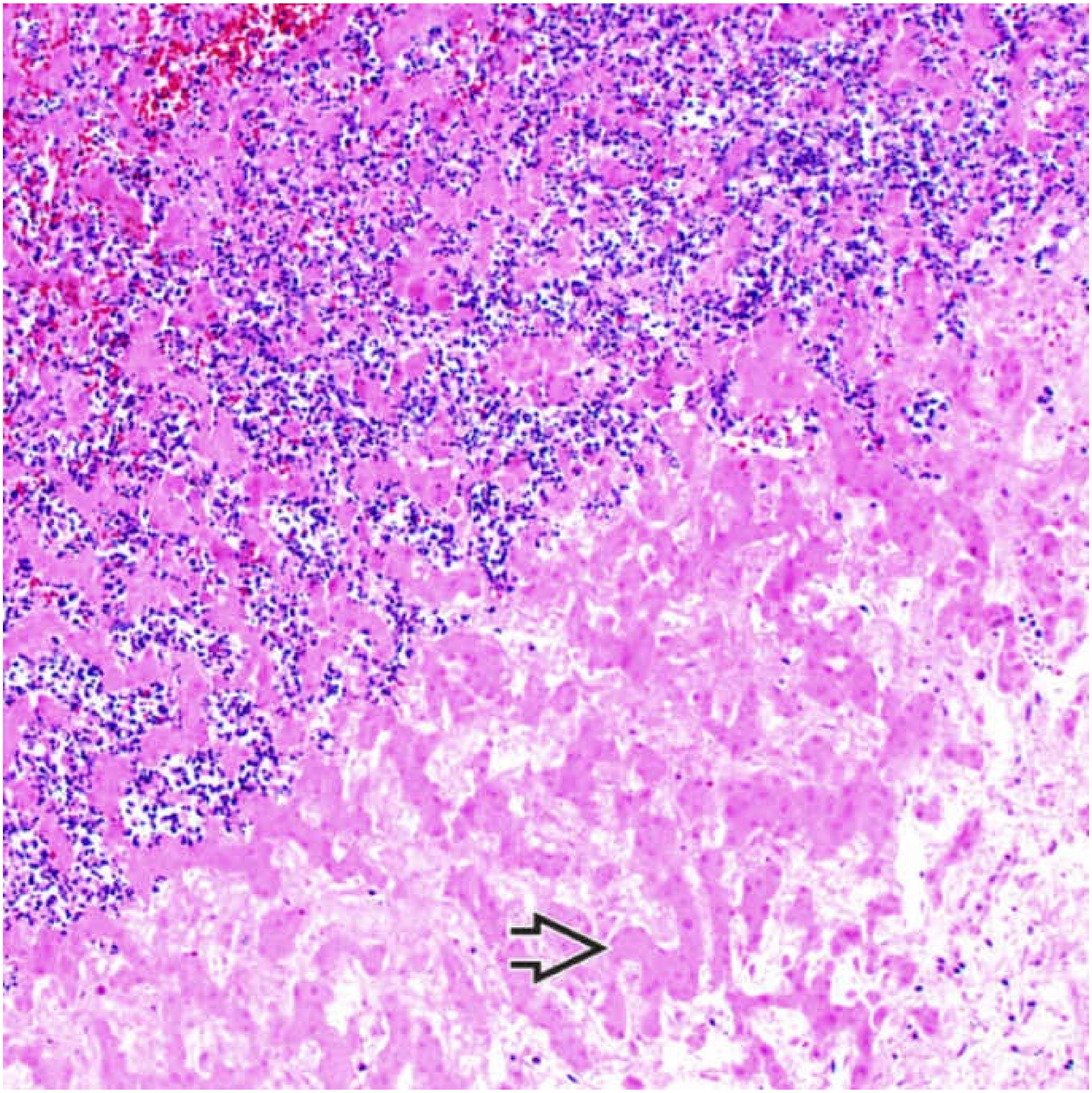
- Culture of abscess contents is critical to diagnosis and management



Gross Appearance
This partial hepatectomy specimen shows 2 large, irregular, yellow-tan abscesses with central green bile-stained necrosis.

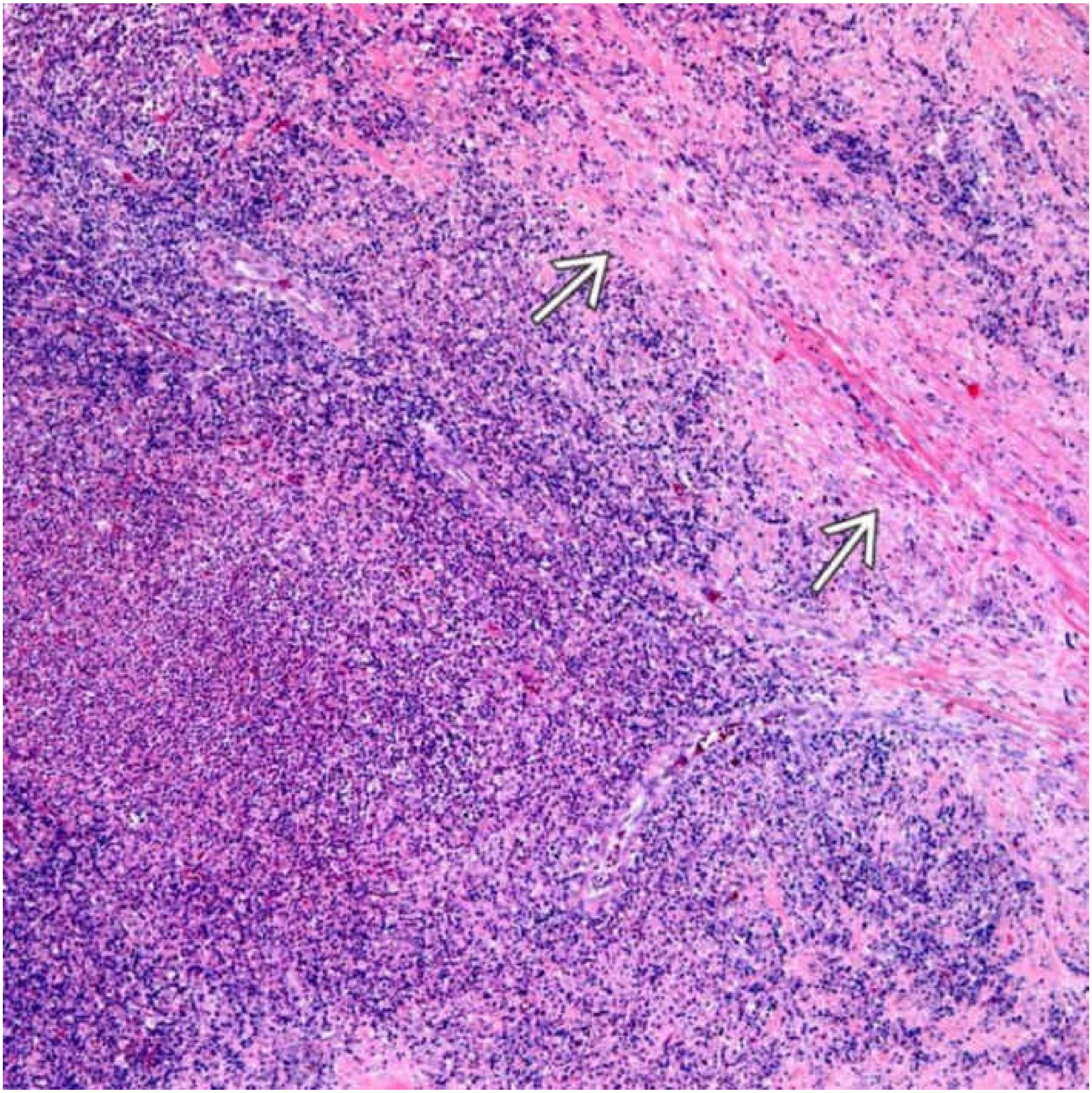


Abscess With Bile
This section of a large liver abscess shows irregular zones of inflammation and necrosis with associated bile. Another smaller abscess containing bile is present at the top of the section ➩ .



Necrosis and Acute Inflammation

In this region of the abscess, necrotic liver parenchyma is identifiable by the ghosts of residual hepatic plate architecture ⇨. The necrotic parenchyma is infiltrated with neutrophils.



Fibrosis
Fibrosis may be very prominent, particularly at the edge of an abscess ⇒, as seen in this actinomycotic abscess. Marked acute and chronic inflammation are also present.

TERMINOLOGY

Definitions

- Infection featuring localized accumulation of pus with surrounding inflammation and fibrosis
  - Occurs via portal vein, arterial system, or bile ducts

ETIOLOGY/PATHOGENESIS

Predisposing Conditions

- Diabetes is major risk factor
  - Other predisposing conditions include malignancy, alcohol abuse, cirrhosis, hypertension, recent surgery, immunosuppression
  - Abscesses secondary to *Yersinia enterocolitica* or *Yersinia pseudotuberculosis* are often associated with underlying hemochromatosis
- Biliary disease
  - Including biliary ischemia secondary to surgery or ablative procedures
- Trauma
- Intraabdominal infections
- Secondary to sepsis
- Significant number are cryptogenic

Epidemiology

- Bacterial abscesses are most common in Western countries
  - *Klebsiella pneumoniae* is now most common pathogen, followed by *Escherichia coli*
    - Both produce formic hydrogenlyase, which can convert acids in abscess into carbon dioxide and hydrogen gas
    - Gas-forming pyogenic abscess carries higher risk of septic shock, bacteremia, and death
  - Other commonly isolated organisms include *Enterococcus* spp., *Streptococcus* spp., and *Pseudomonas* spp.
  - Anaerobes are isolated in up to 25% of cases
    - Most commonly microaerophilic *Streptococci*, *Bacteroides fragilis*, *Fusobacterium necrophorum*, and *Clostridia* spp.
    - *Actinomyces* spp. can be associated with formation of sinus tracts and solitary masses that mimic malignancy
  - Rare isolates include *Francisella tularensis*, *Burkholderia pseudomallei* (melioidosis), *Brucella* spp. (particularly *B. suis*), and *Listeria monocytogenes*
  - Fungi (i.e., *Candida* and *Aspergillus)* are found in 15% of cases
  - At least 1/3 of cases are polymicrobial
- Peak incidence in patients 55-60 years old; male predominance

CLINICAL ISSUES

Presentation

- Fever, chills, right upper quadrant pain
  - Nonspecific signs/symptoms such as diarrhea, nausea, vomiting, jaundice, right pleural effusion also common

Laboratory Tests

- Elevated WBC count, ESR, CRP, bilirubin, alkaline phosphatase, transaminases
- Hypoalbuminemia and anemia also common

Treatment

- Antibiotic therapy
- Drainage
- Surgery is occasionally necessary

Prognosis

- Mortality ~ 15%
  - Complications include spread of infection (endophthalmitis, meningitis, osteomyelitis, pyelonephritis, and pneumonia)
  - Main risk factors for metastatic infection are diabetes and infection with *K. pneumonia*

IMAGING

Primary Method of Diagnosis

- Ultrasound &/or CT
  - Confirmatory needle aspiration useful for both diagnosis and culture

MACROSCOPIC

General Features

- Most are solitary
  - Multiple abscesses occur in 25-45% of cases
- Most occur in right lobe (70%); left lobe or bilateral disease is less common
- Appear as irregular area of softening with central liquefactive necrosis and green discoloration with variable surrounding fibrosis

MICROSCOPIC

Histologic Features

- Collection of neutrophils with fibrin, bile, or necrotic debris
- Variably present fibrosis surrounding abscess
- Additional findings may be seen depending on causative organism, such as sulfur granules in *Actinomyces* infection
- Cholangitis

Ancillary Studies

- Histochemical stains for organisms (Gram, GMS, acid-fast, PAS, and Steiner stains)
- Culture of abscess contents; blood culture may also be useful

DIFFERENTIAL DIAGNOSIS

Other Causes of Hepatic Abscess

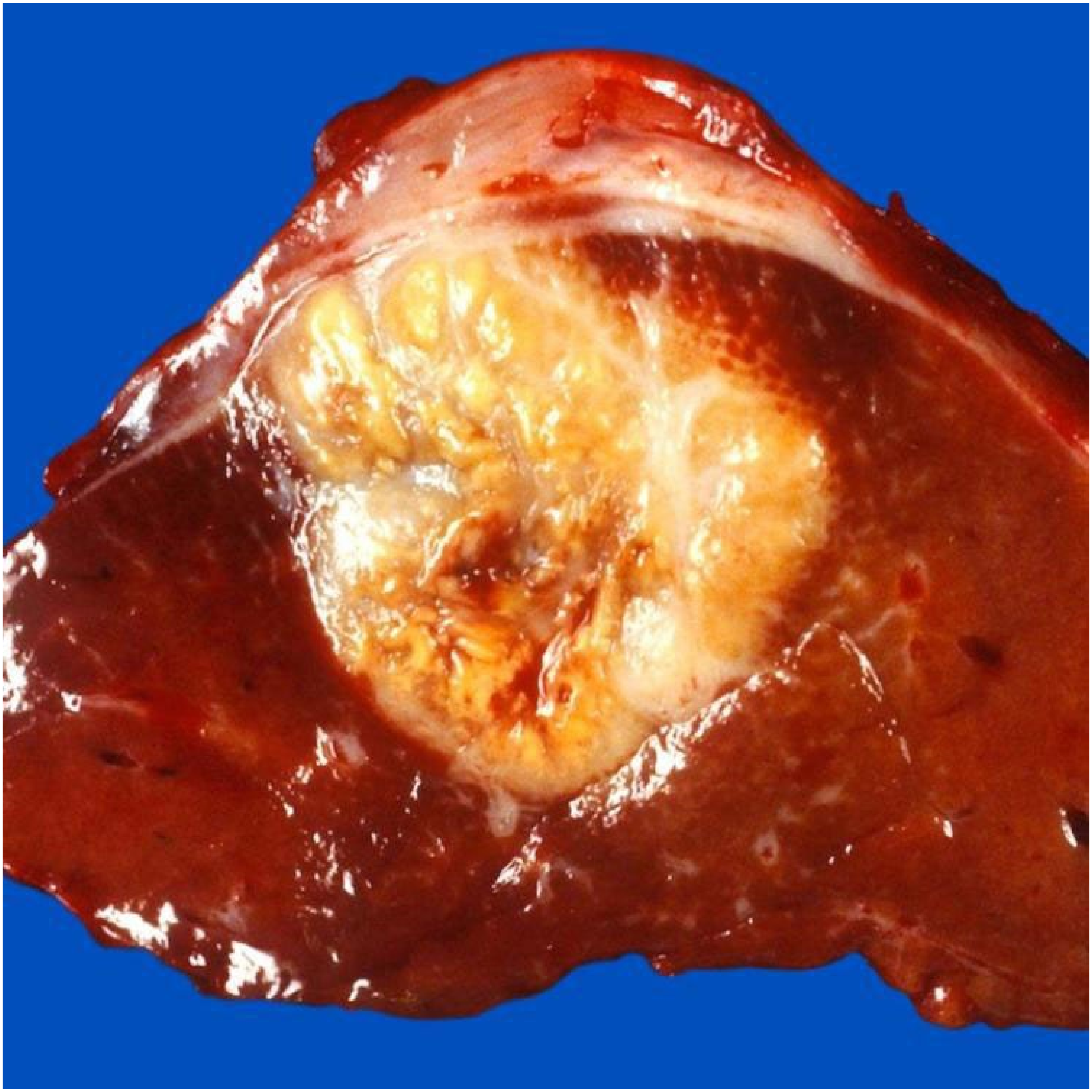
- Tuberculosis, amebiasis, ascariasis

Recurrent Pyogenic Cholangitis

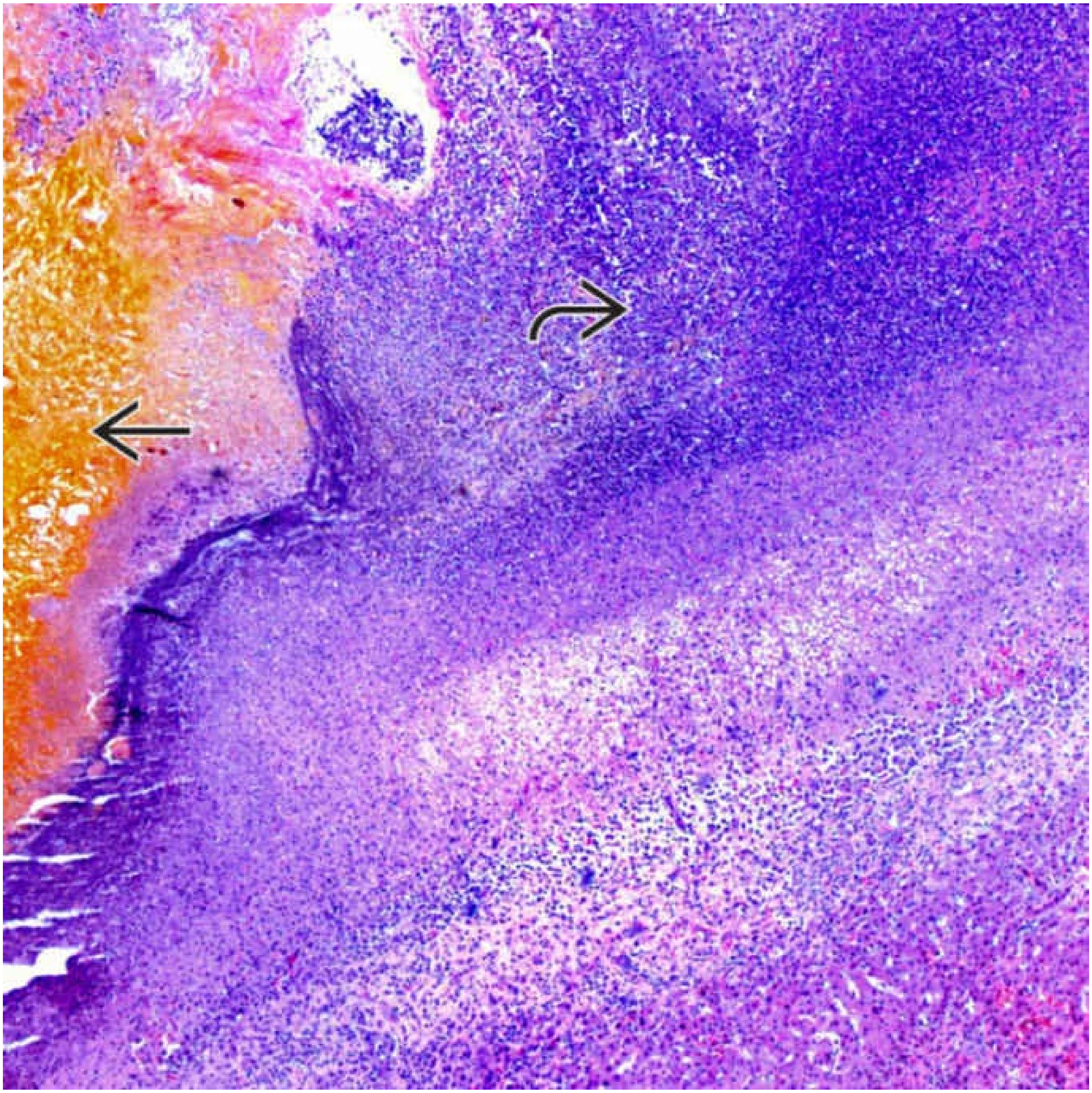
- Patients from Far East or Asian immigrants
- Recurrent attacks of suppurative cholangitis with hepatic stones
- Associated with biliary flukes

Tumor

- Symptoms, imaging can mimic malignancy

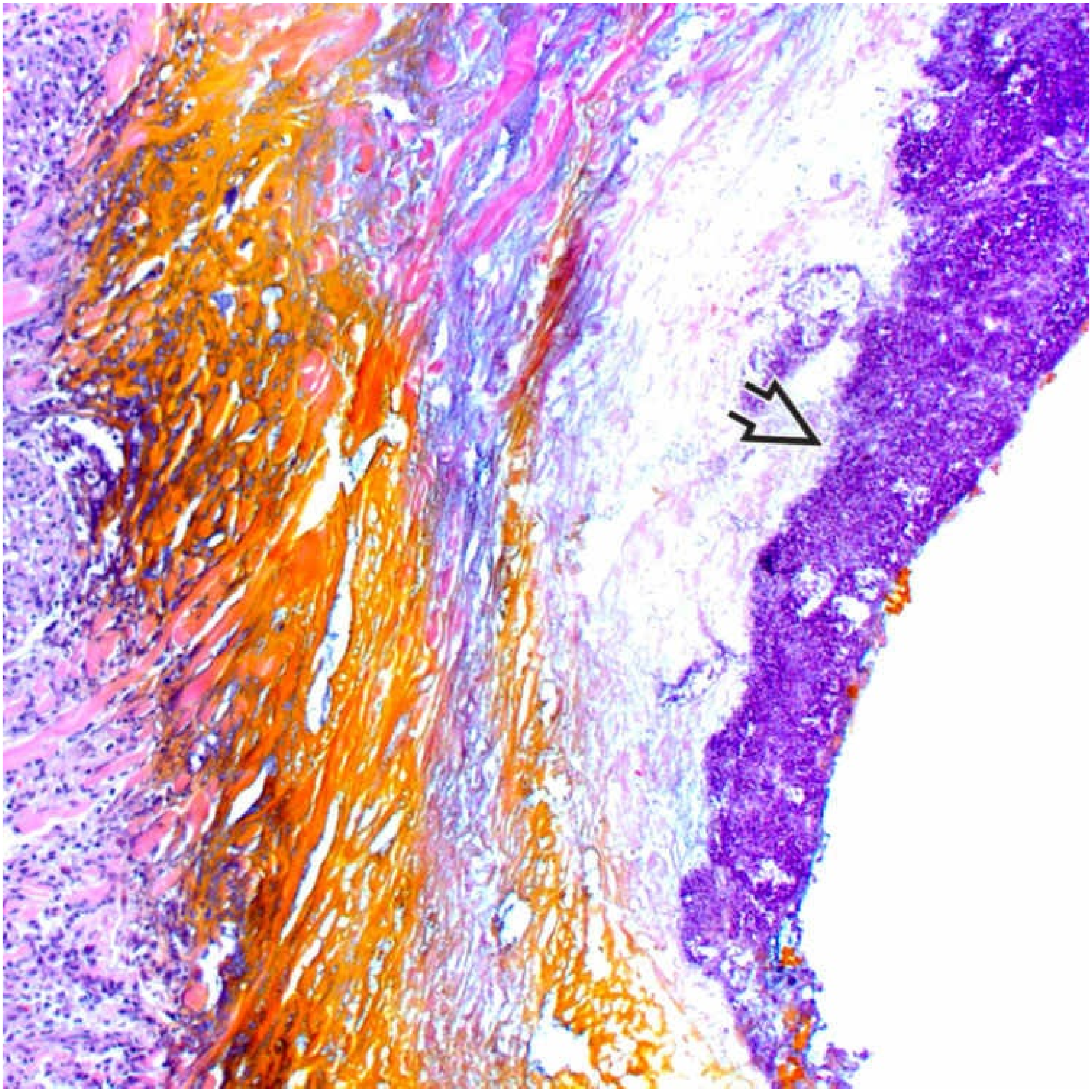


Solitary Abscess
Hepatic abscesses are most commonly solitary, as seen here. Abscesses with abundant fibrosis can mimic tumors on imaging studies. (Courtesy G.F. Gray, Jr., MD.)



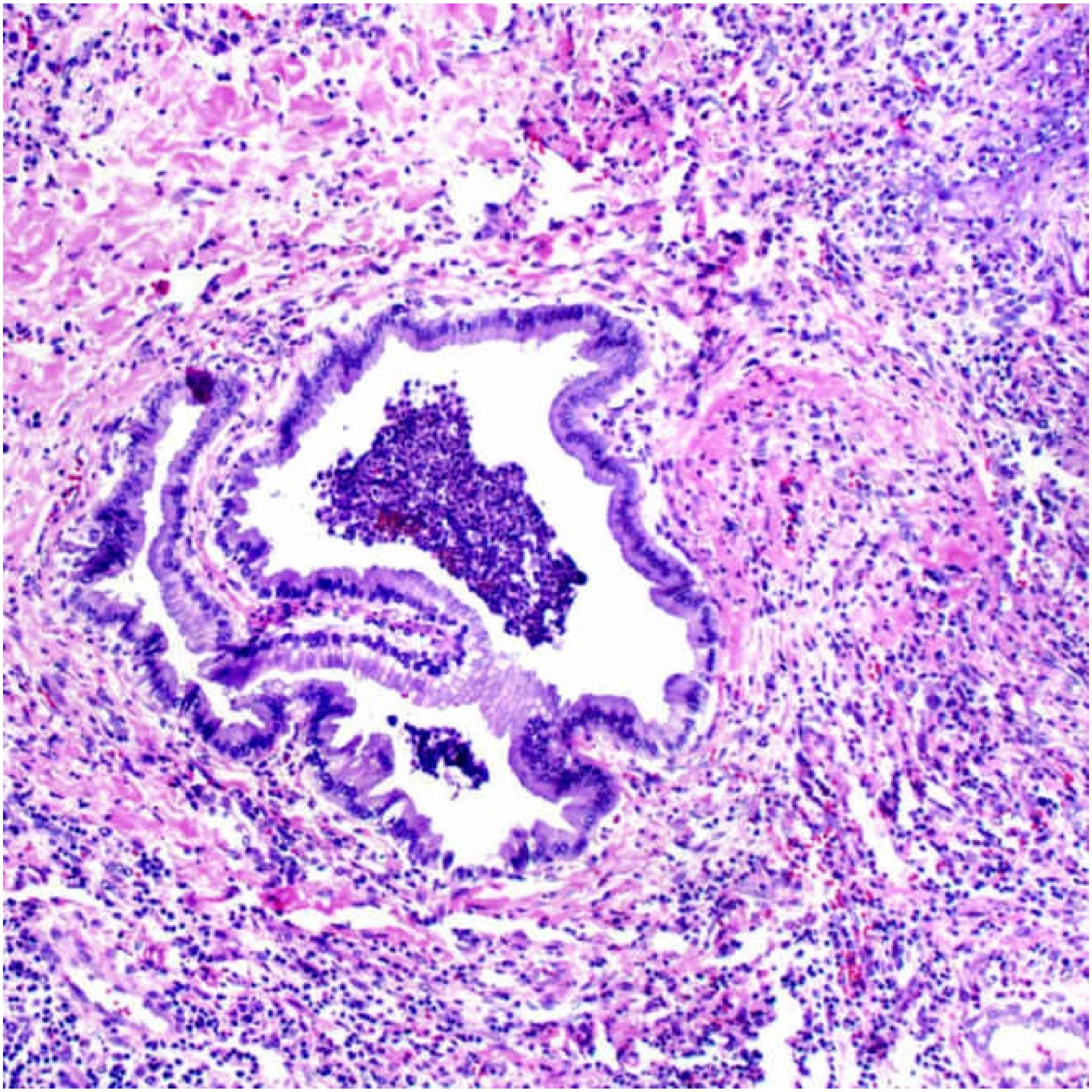
Pus, Fibrin, and Bile

This large liver abscess contains abundant acute inflammation ↱, fibrin, necrotic debris, and bile →.
Intact liver parenchyma is seen in the lower right corner.



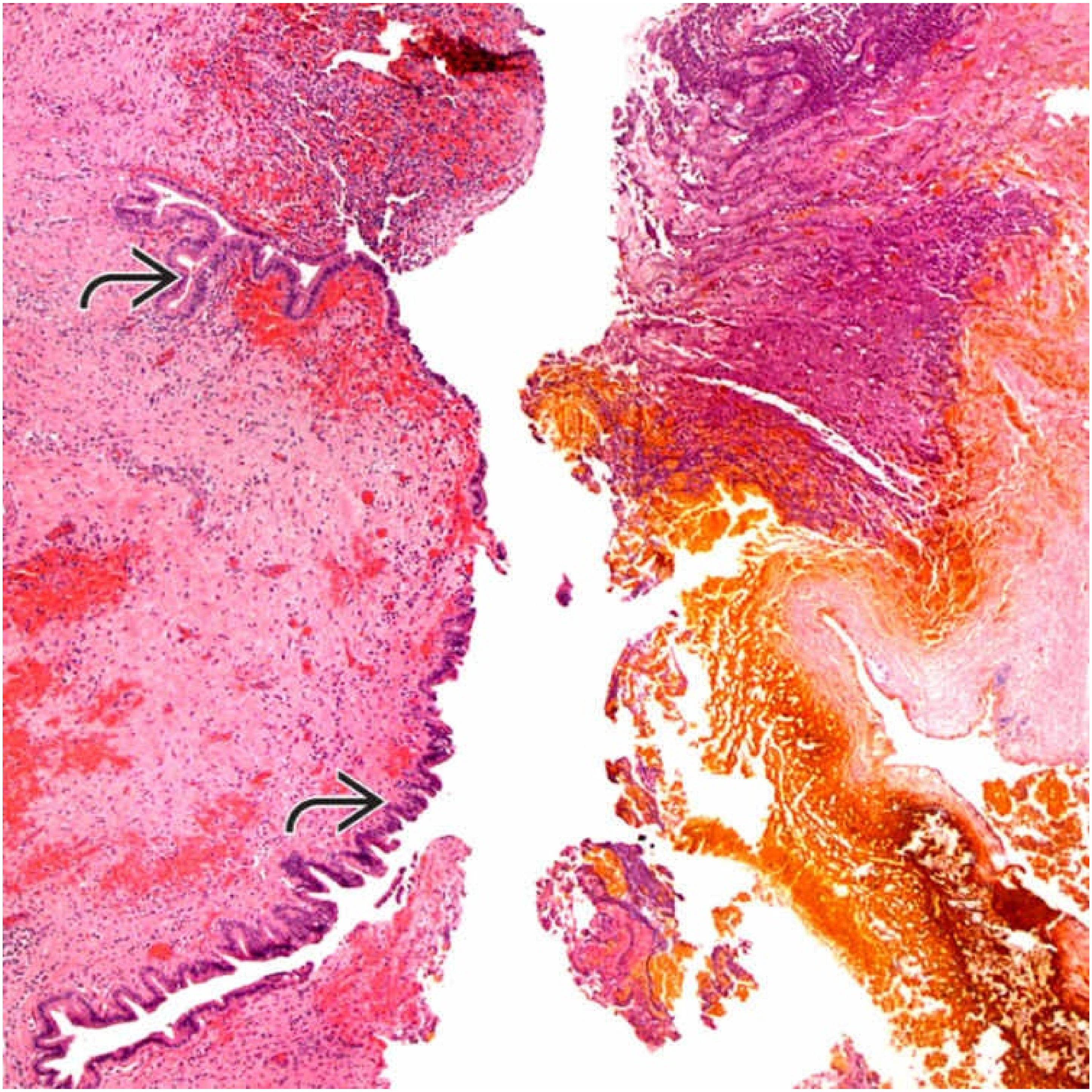
Abscess With Bile

Bile, fibrin, and bacteria ⇨, sometimes abundant, are often present within the abscess.

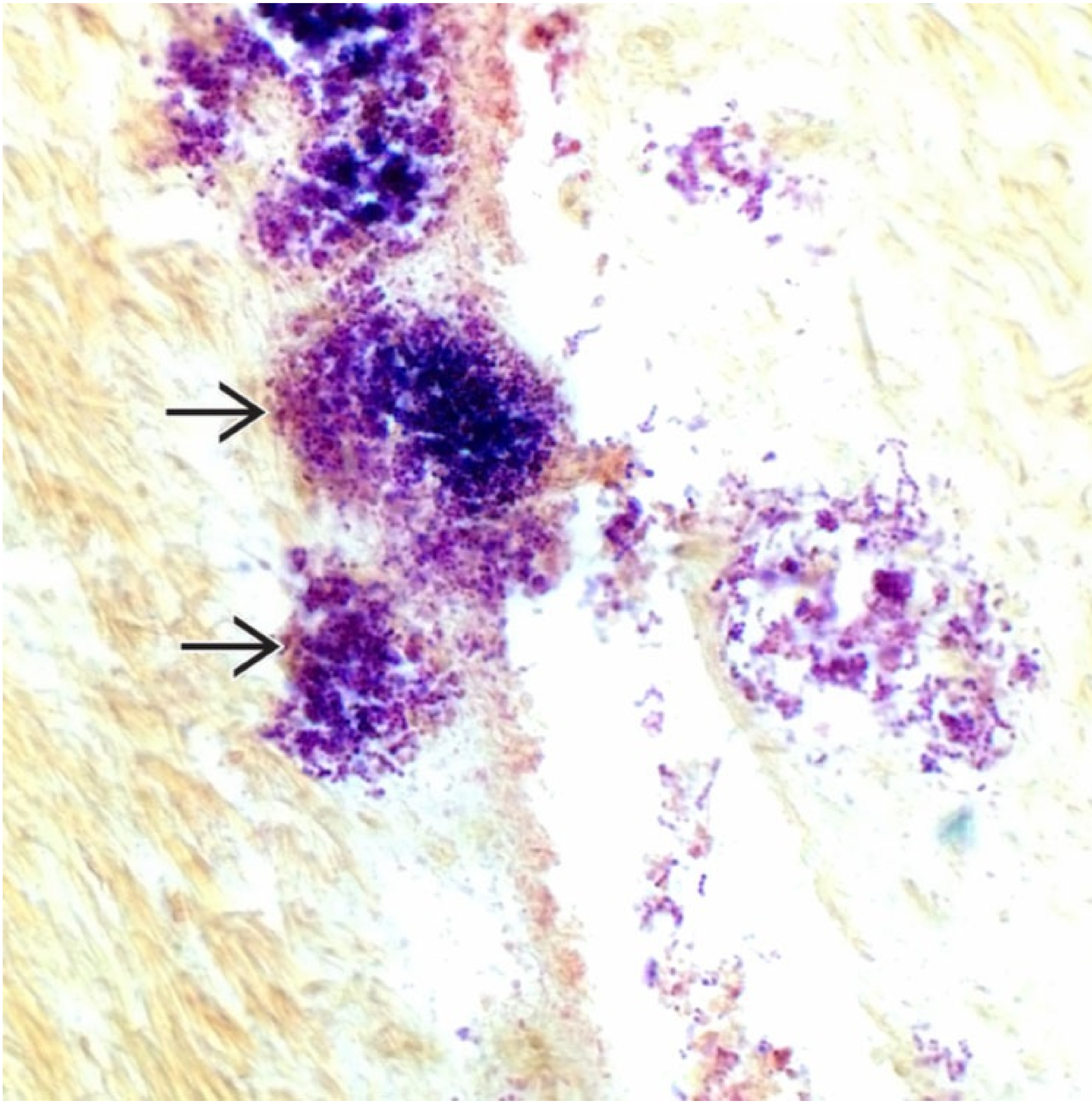


Suppurative Cholangitis

A focus of suppurative cholangitis (accumulation of neutrophils and fibrin within a duct) is present directly adjacent to a pyogenic abscess. Cholangitis may occur secondary to the inflammation in the liver, or abscesses may result from suppurative cholangitis.

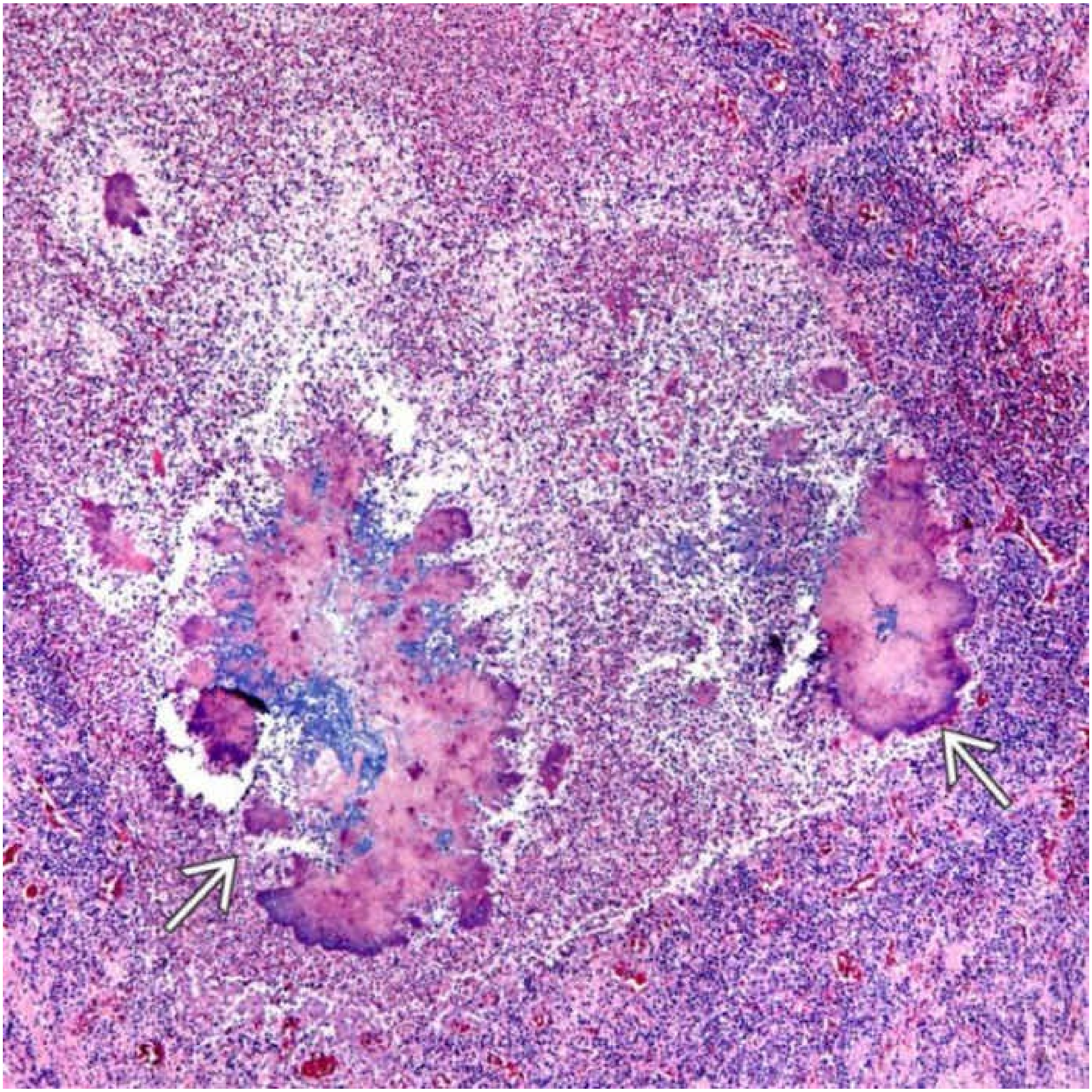


Abscess With Adjacent Duct
This large liver abscess containing bile, fibrin, and neutrophils (right) is directly adjacent to an inflamed bile duct, suggesting origin from suppurative cholangitis.

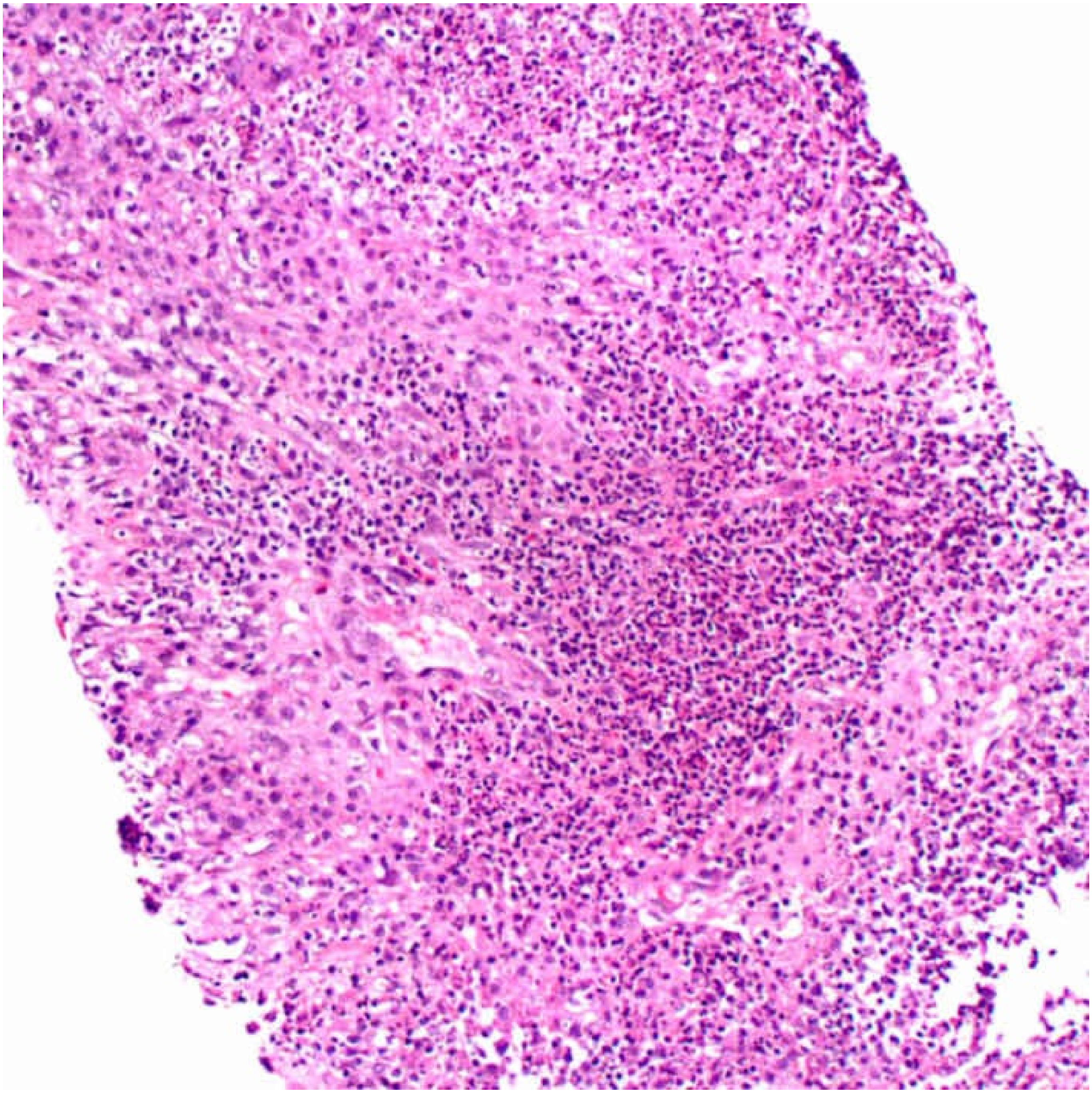


Tissue Gram Stain

A tissue Gram stain shows clusters of gram-positive cocci → in this liver abscess that yielded Enterococcus on microbiologic culture of aspirated purulent material.

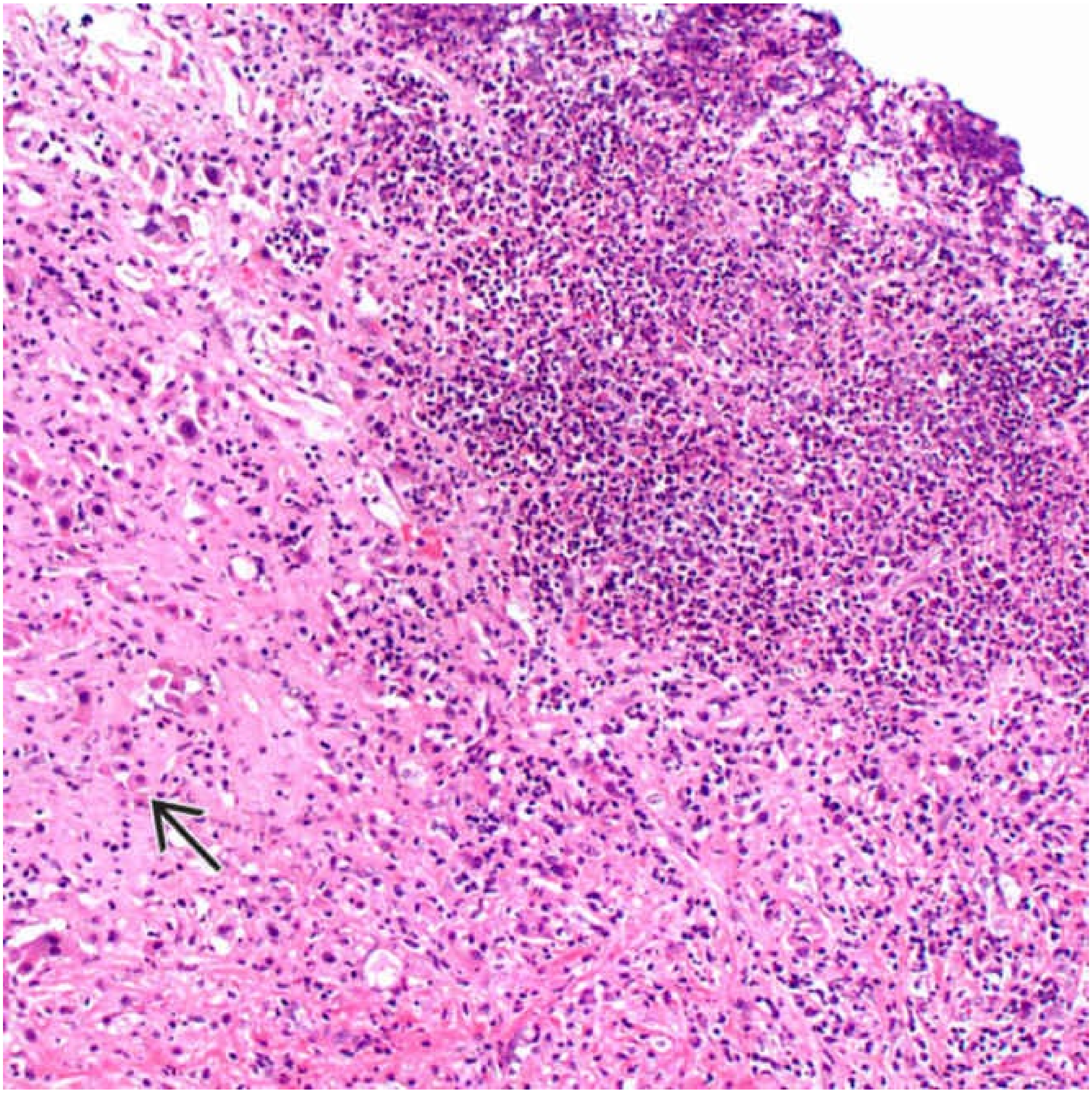


Actinomycotic Abscess
This abscess secondary to actinomycosis shows sulfur granules ⇒ in the center of marked acute and chronic inflammation (abscess).



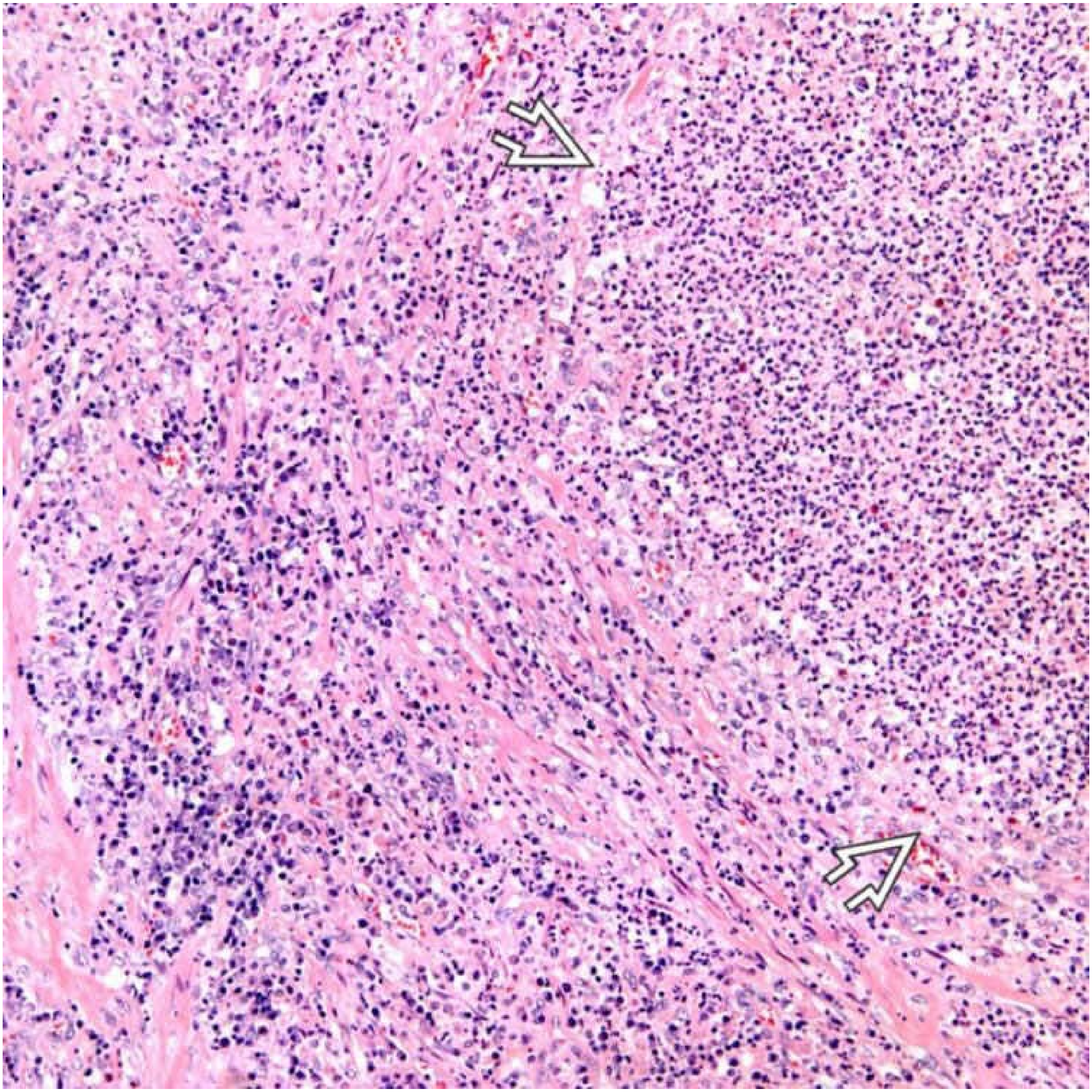
Neutrophilic Inflammation

Biopsies of hepatic abscesses may show only neutrophilic inflammation and necrosis, without viable hepatic parenchyma. This is an important diagnostic consideration when a needle biopsy yields only acute inflammation.



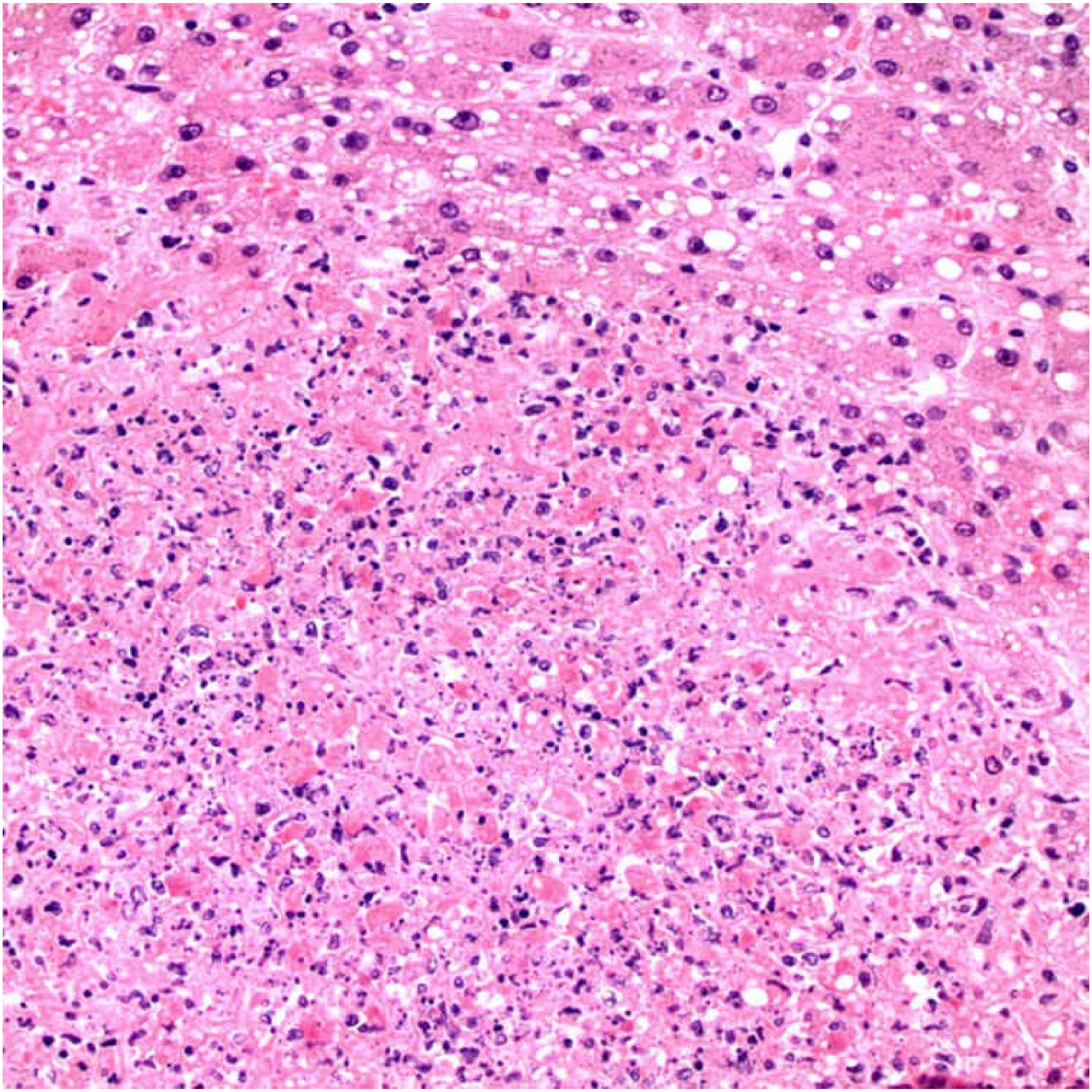
Neutrophilic Inflammation

This biopsy of a pyogenic abscess shows a dense accumulation of neutrophils, surrounded by chronic inflammatory cells, edema, and necrosis. There are rare entrapped hepatocytes →.



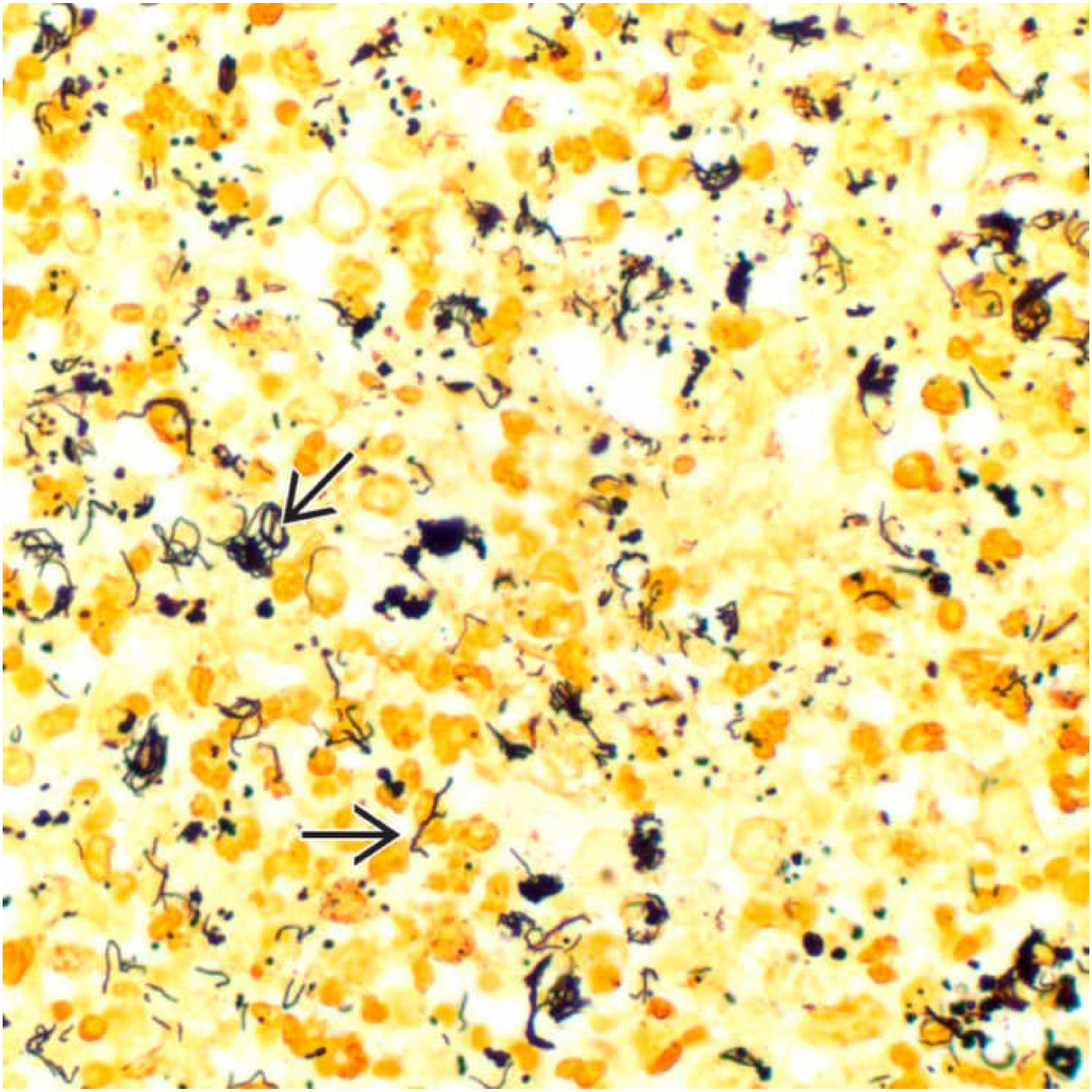
Dense Fibrosis

Some pyogenic abscesses have a very dense rim of fibrosis at the periphery. Note the neutrophilic abscess at the right of the field ⇨ .



Listeria Abscess

This well-circumscribed, pyogenic abscess secondary to Listeria features abundant necrosis with admixed acute inflammation and apoptotic nuclear debris. The adjacent hepatocytes contain steatosis.



Steiner Stain

A Steiner stain shows a mixture of bacteria, including long slender rod-shaped organisms →, obtained from a polymicrobial abscess; culture also yielded mixed anaerobes.

SELECTED REFERENCES

1.Lardière-Deguelte, S, et al. Hepatic abscess: Diagnosis and management. *J Visc Surg*. 2015; 152(4):231–243.

2.Liu, Y, et al. An Increasing Prominent Disease of Klebsiella pneumoniae Liver Abscess: Etiology, Diagnosis, and Treatment. *Gastroenterol Res Pract*. 2013; 2013:258514.

4. Ruiz-Hernández, JJ, et al. Pyogenic liver abscesses: mortality-related factors. *Eur J Gastroenterol Hepatol*. 2007; 19(10):853–858.

5. Thomsen, RW, et al. Diabetes mellitus and pyogenic liver abscess: risk and prognosis. *Clin*

Infect Dis. 2007; 44(9):1194–1201.
6. Rahimian, J, et al. Pyogenic liver abscess: recent trends in etiology and mortality. *Clin Infect Dis*. 2004; 39(11):1654–1659.
8. Zibari, GB, et al. Pyogenic liver abscess. *Surg Infect (Larchmt)*. 2000; 1(1):15–21.

3. Fang, CT, et al. Klebsiella pneumoniae genotype K1: an emerging pathogen that causes septic ocular or central nervous system complications from pyogenic liver abscess. *Clin Infect Dis*. 2007; 45(3):284–293.
7. Bergmann, TK, et al. Multiple hepatic abscesses due to Yersinia enterocolitica infection secondary to primary haemochromatosis. *Scand J Gastroenterol*. 2001; 36(8):891–895.

Sepsis in Liver

KEY FACTS

Terminology

- Spectrum of hepatic injury in patients with sepsis or bacteremia

Etiology/Pathogenesis

- Usually caused by sepsis from underlying bacterial pneumonia or intraabdominal infection
  - Most often gram-negative infection
- Mechanisms uncertain but probably involve decreased activity and expression of canalicular and sinusoidal transporters

Clinical Issues

- Patients are systemically ill and typically jaundiced
- Enzyme elevations may be hepatocellular, cholestatic, or mixed

Microscopic

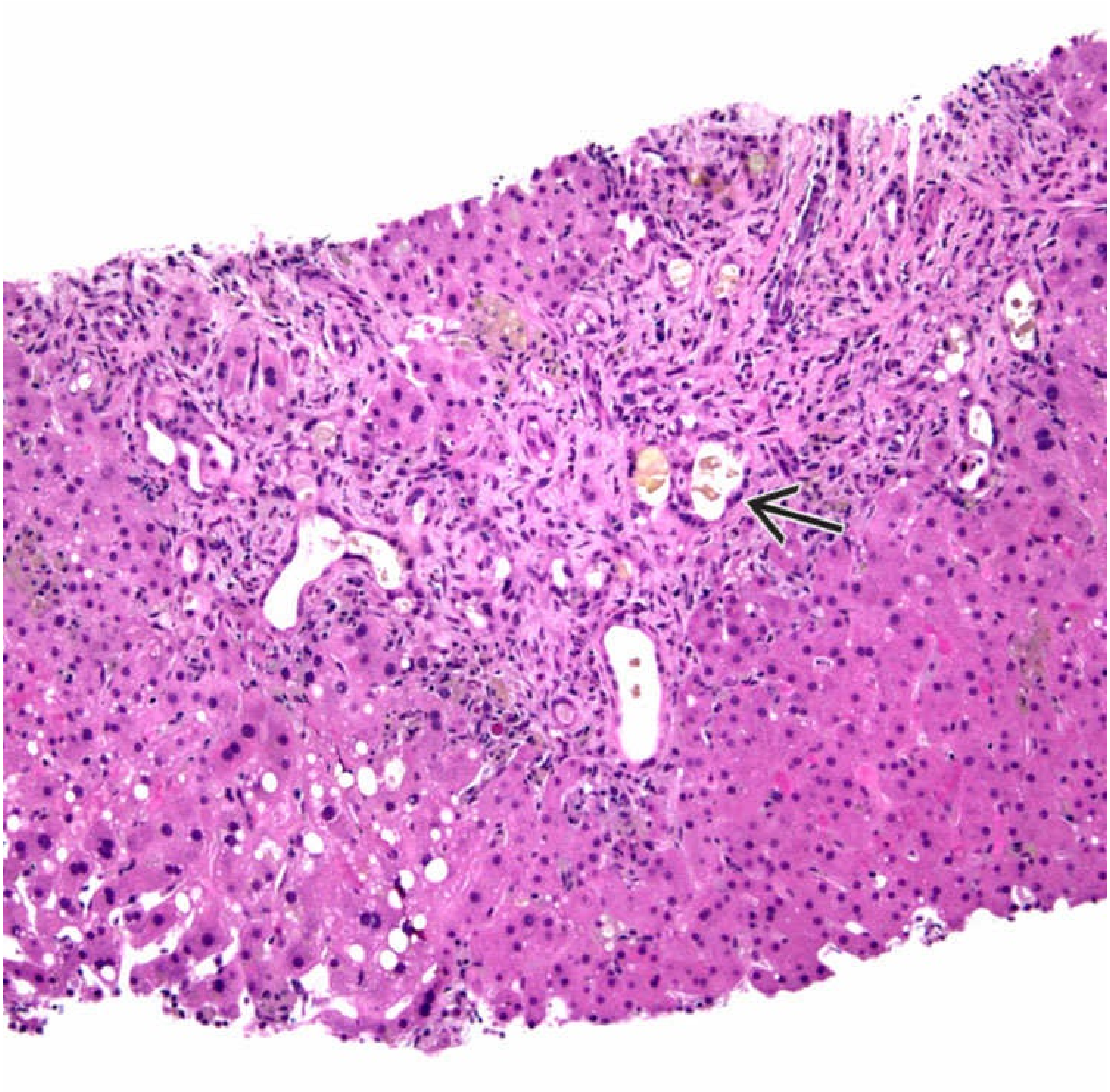
- Ductular cholestasis pattern strongly associated with sepsis
  - Ductular reaction at perimeter of portal tracts with dilated profile, flattened epithelium, inspissated bile
- Variably present neutrophilic inflammation
- Canalicular cholestasis also common
  - May lack significant attendant inflammation, especially in infants and children

Top Differential Diagnoses

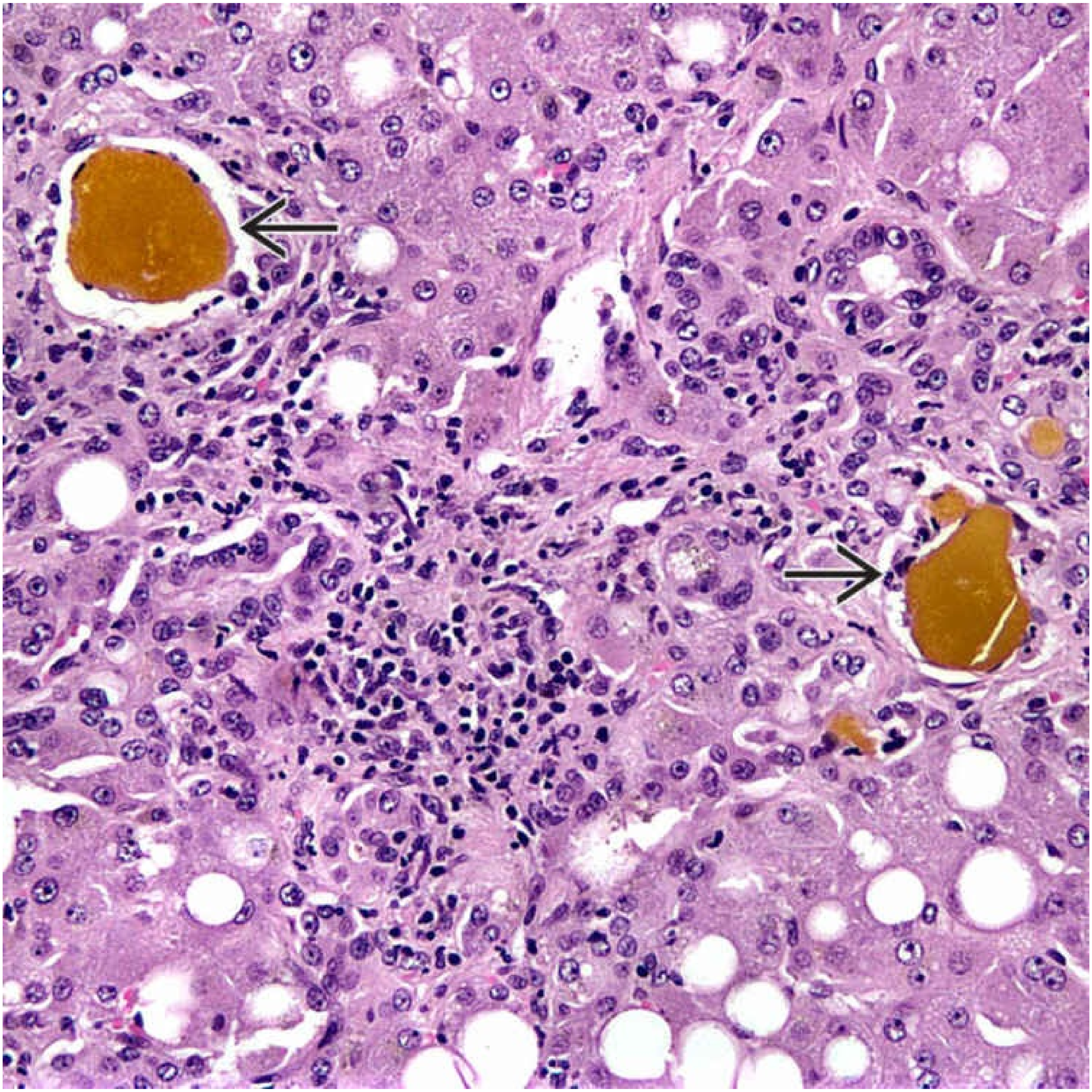
- Large bile duct obstruction
- Total parenteral nutrition

Diagnostic Checklist

- Many entities in differential diagnosis can coexist along with sepsis and may confound histologic picture
  - Blood cultures should be drawn in severely ill patients with these findings on biopsy

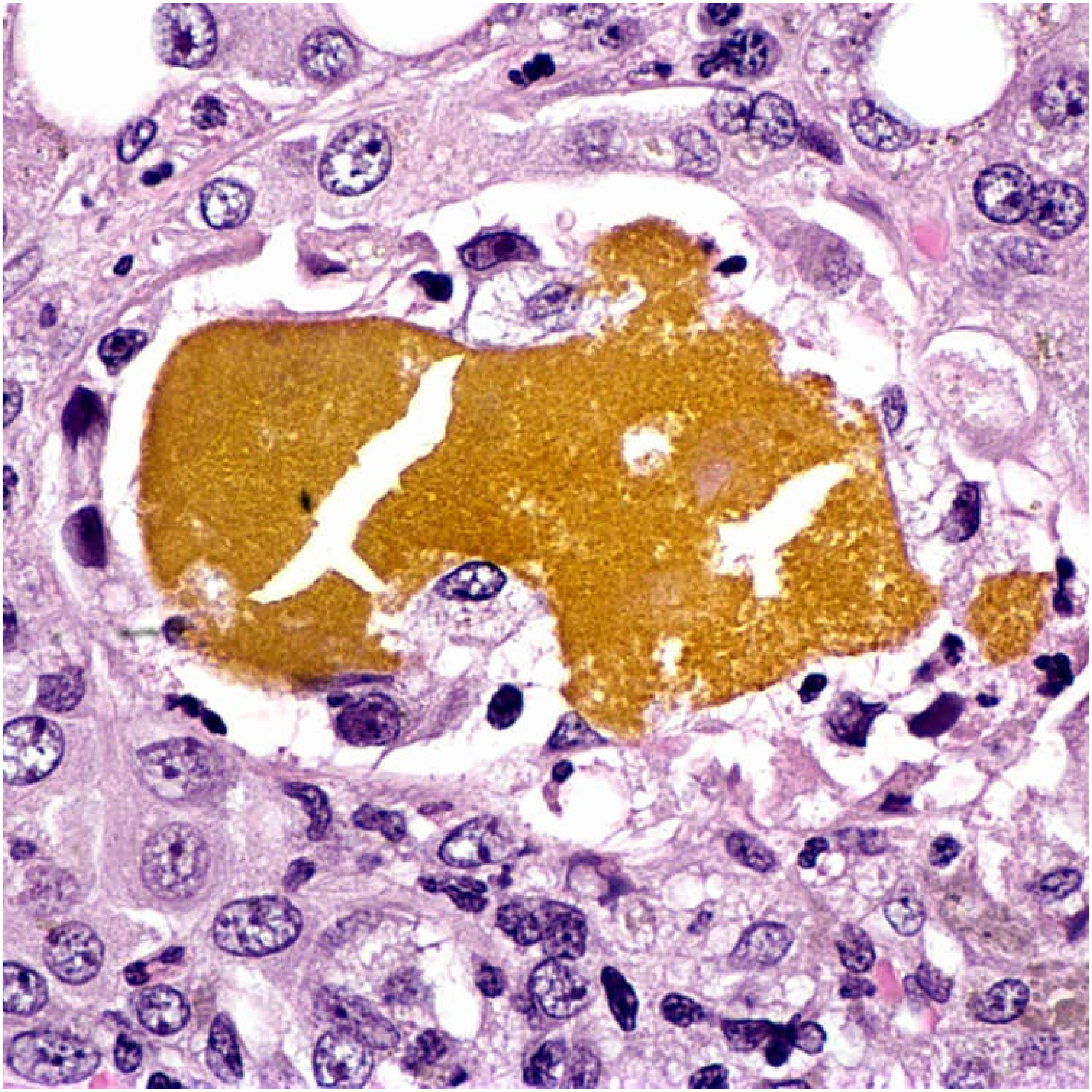


Ductular Dilatation and Inspissated Bile
A low-power photograph of a liver biopsy specimen in a septic patient shows expanded portal tracts with ductular reaction. Many of the ductules are dilated and contain inspissated bile →. The lobule shows reactive changes.

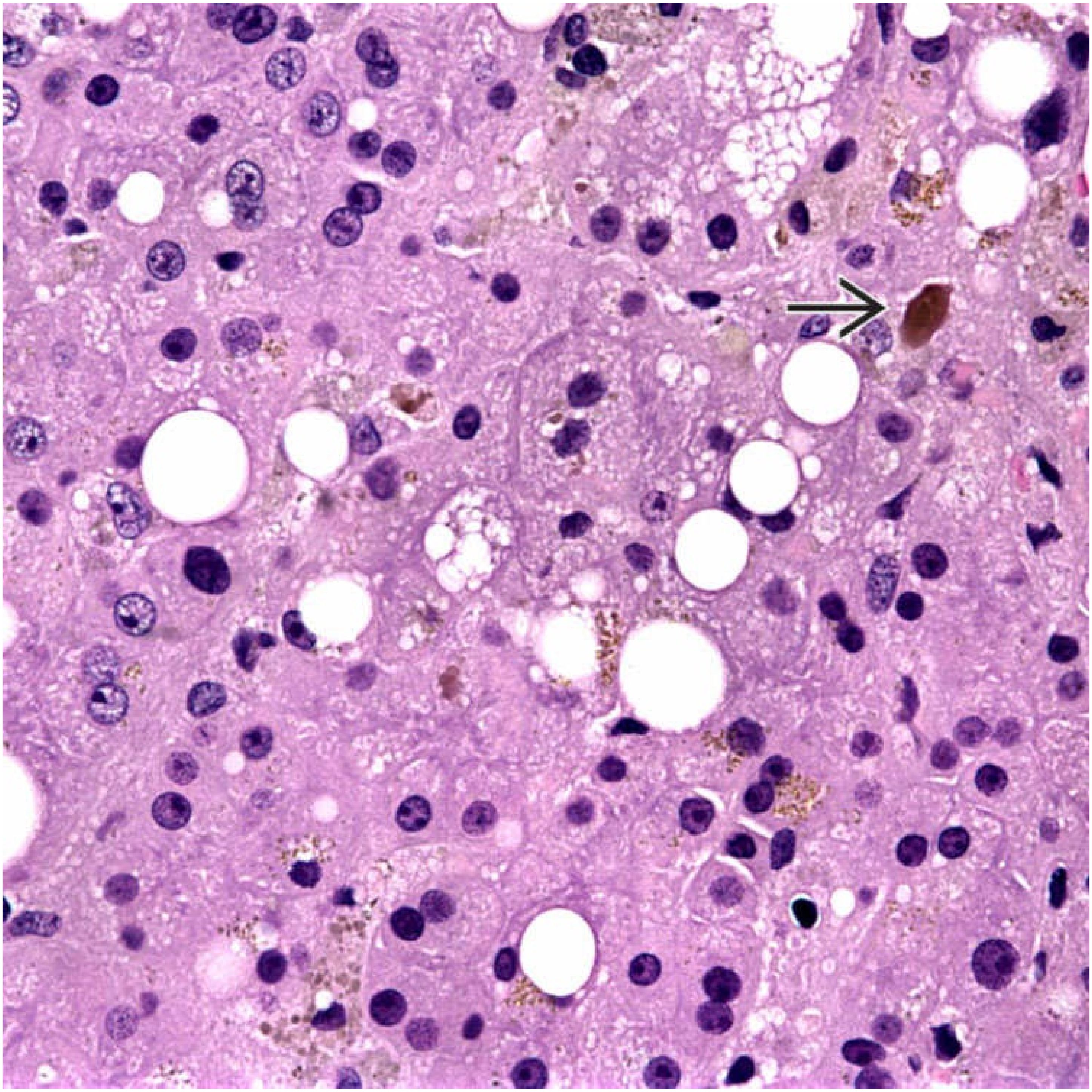


Ductular Cholestasis

This portal tract has ductular reaction at the periphery. The ductules contain dense, inspissated bile → (ductular cholestasis). Neutrophils may be variably present.



Inspissated Bile
This high-power view of a bile ductule illustrates the flattened, atrophic epithelium and dense, inspissated bile that are typical of ductular cholestasis.



Canalicular Cholestasis
Canalicular cholestasis → without significant accompanying inflammation, or “pure” cholestasis, is common in patients with sepsis/systemic infection, particularly infants and children.

TERMINOLOGY

Definitions

- Spectrum of hepatic injury in patients with sepsis or bacteremia

ETIOLOGY/PATHOGENESIS

Infectious Agents

- Systemic infection, usually gram-negative sepsis
  - Most common underlying infectious processes
  - – Bacterial pneumonia
  - – Intraabdominal suppurative infection
- Mechanism uncertain
  - Presumably, bacterial endotoxins interfere with normal flow of bile and canalicular function
    - – Decreased activity and expression of both canalicular and sinusoidal transporters of bile acids and organic anions

CLINICAL ISSUES

Presentation

- Patients are systemically ill from sepsis/bacteremia
  - May be in shock
- Jaundice is common
  - Typically resolves with control of underlying infection

Laboratory Tests

- Hyperbilirubinemia and elevated alkaline phosphatase
  - May precede positive blood cultures
- Variably elevated transaminases

Treatment

- Treatment of underlying infection
- Supportive care

Prognosis

- Depends on severity of underlying infection
- Patients are often severely ill with poor prognosis

MACROSCOPIC

General Features

- Variably present hepatomegaly

MICROSCOPIC

Histologic Features

- Cholestasis
  - Ductular cholestasis
    - Ductular reaction at perimeter of portal tracts with inspissated bile
    - Ductules may be dilated, with atrophic and flattened epithelium
    - Periductular neutrophilic infiltrate
  - Centrilobular canalicular cholestasis
    - "Pure" cholestasis with no significant inflammation is fairly common in sepsis, especially in infants and children
    - Hepatocellular cholestasis may be present as well
- Neutrophilic inflammation
  - Portal &/or lobular
  - Variably present microabscesses
- Additional findings
  - Focal hepatocyte necrosis
  - Centrilobular &/or midzonal fatty change, usually microvesicular
  - Kupffer cell hyperplasia
  - Hepatocellular reactive changes
- Many cases have mixed features combining several features above
- Patients in septic shock may have ischemic necrosis, particularly in perivenular distribution

DIFFERENTIAL DIAGNOSIS

Large Bile Duct Obstruction

- Histologic features may be very similar
  - Important to recognize cholestatic pattern of sepsis so that patients are not subjected to unnecessary invasive procedures to rule out obstruction
- Obstruction generally does not feature ductular cholestasis
- May need clinical history and imaging studies to differentiate

Adverse Drug Reaction

- May show ductular cholestasis or "pure" cholestasis, both of which can mimic sepsis
- Clinical history (particularly medication history) necessary to resolve

Total Parenteral Nutrition

- May also show ductular cholestasis
- Patients have history of total parenteral nutrition

Other Infectious Processes

- Primary viral, fungal, or bacterial infections of liver may feature cholestasis

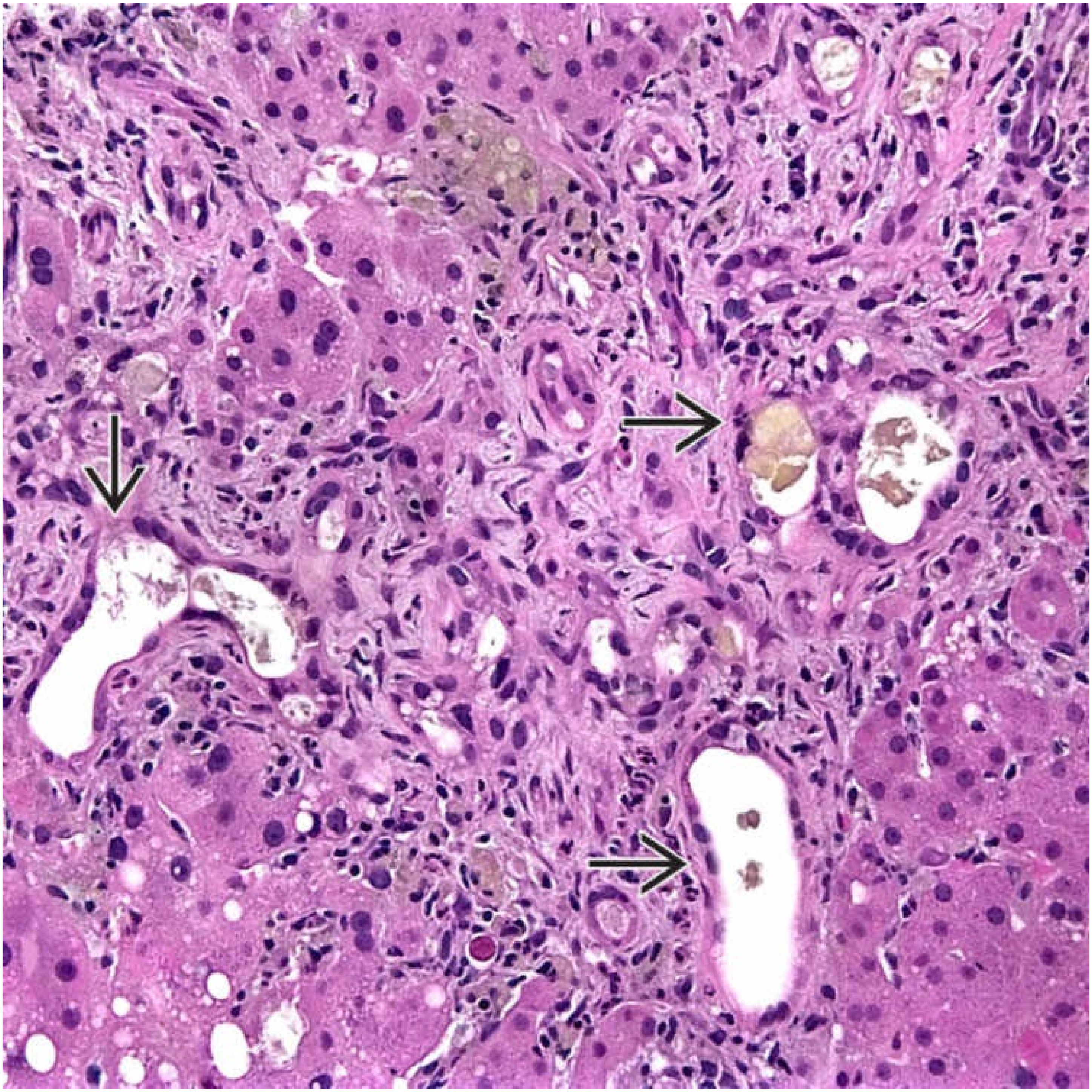
Biliary Atresia in Newborns

- May also show ductular cholestasis
- Clinical history/imaging necessary to resolve

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Sepsis produces several different histologic patterns in liver
- Many entities in differential diagnosis above can coexist along with sepsis and may confound histologic picture



Hematoxylin & eosin shows a portal tract containing mixed inflammation with numerous eosinophils.
Proliferated bile ductules are present at the edge of the portal tract, containing inspissated bile →.

SELECTED REFERENCES

1.Hawker, F. Liver dysfunction in critical illness. *Anaesth Intensive Care*. 1991; 19(2):165–181.
2.Cone, LA, et al. Clinical and bacteriologic observations of a toxic shock-like syndrome due to Streptococcus pyogenes. *N Engl J Med*. 1987; 317(3):146–149.
3.Banks, JG, et al. Liver function in septic shock. *J Clin Pathol*. 1982; 35(11):1249–1252.
4.Caruana, JA, Jr., et al. Functional and histopathologic changes in the liver during sepsis. *Surg Gynecol Obstet*. 1982; 154(5):653–656.
5.Lefkowitch, JH. Bile ductular cholestasis: an ominous histopathologic sign related to sepsis and "cholangitis lenta". *Hum Pathol*. 1982; 13(1):19–24.

6. Jaundice due to bacterial infection. *Gastroenterology*. 1979; 77(2):362–374.

Mycobacterium tuberculosis

KEY FACTS

Terminology

- Infection by *Mycobacterium tuberculosis* (MTB)
  - Hepatic TB seen in ~ 1% of patients with active TB
  - More common in HIV(+) patients

Etiology/Pathogenesis

- Transmission typically by inhalation
  - Can reach liver by hematogenous spread or direct spread from GI tract

Clinical Issues

- Liver is usually involved as part of disseminated TB
  - Most common symptoms overall are hepatomegaly, fever, abdominal pain, weight loss
  - Tuberculoma/localized disease can mimic neoplasm and compress biliary tract, vessels
  - Mortality ranges from 10-40%
  - Worse prognosis with immune compromise, drug-resistant organisms

Microscopic

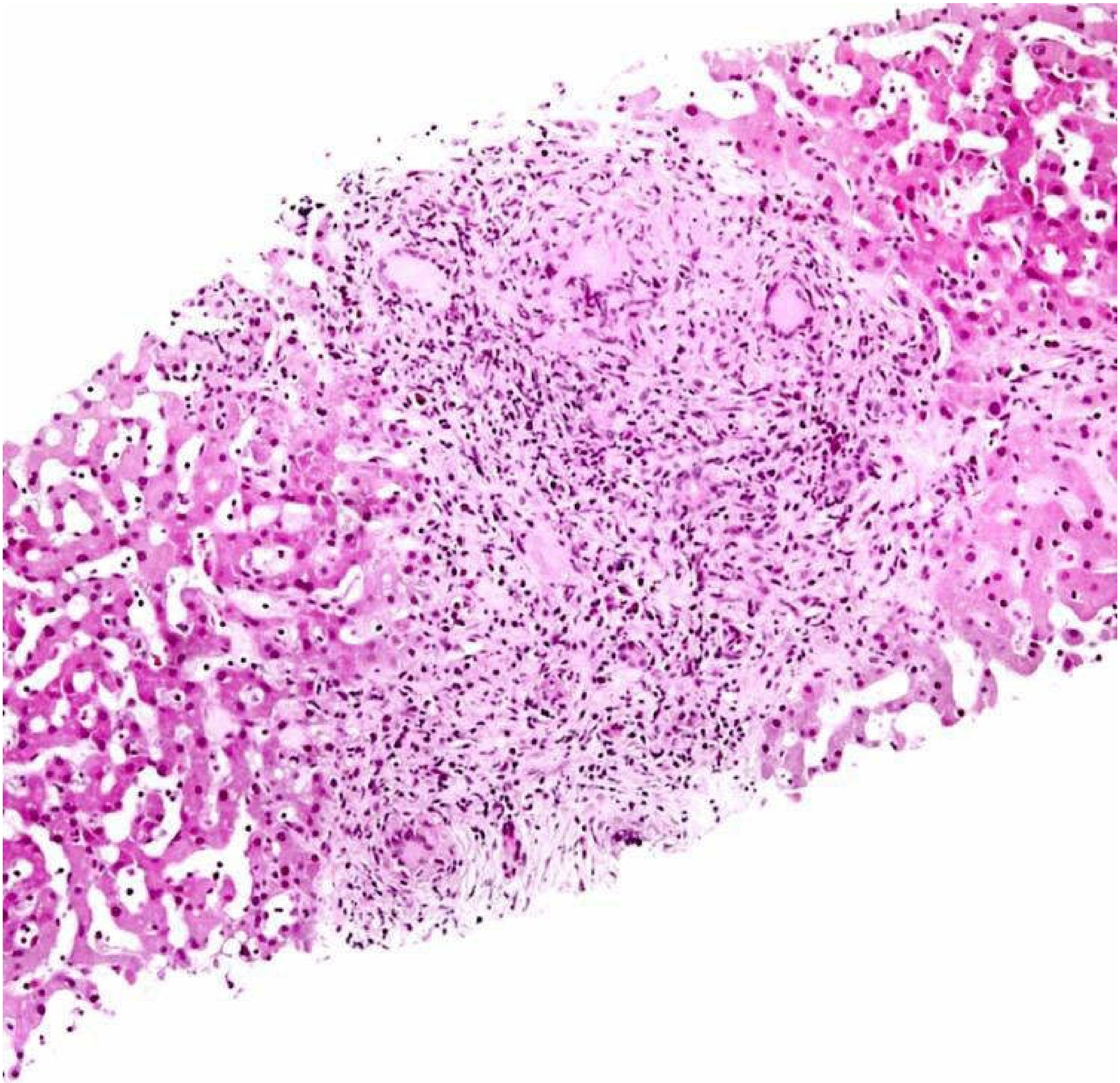
- Numerous granulomas ± central necrosis
  - Coalescence of granulomas can produce tuberculoma
- Immunocompromised patients may have poorly developed granulomas or abscesses
- Acid-fast stains (+) in up to 60% of cases

Ancillary Tests

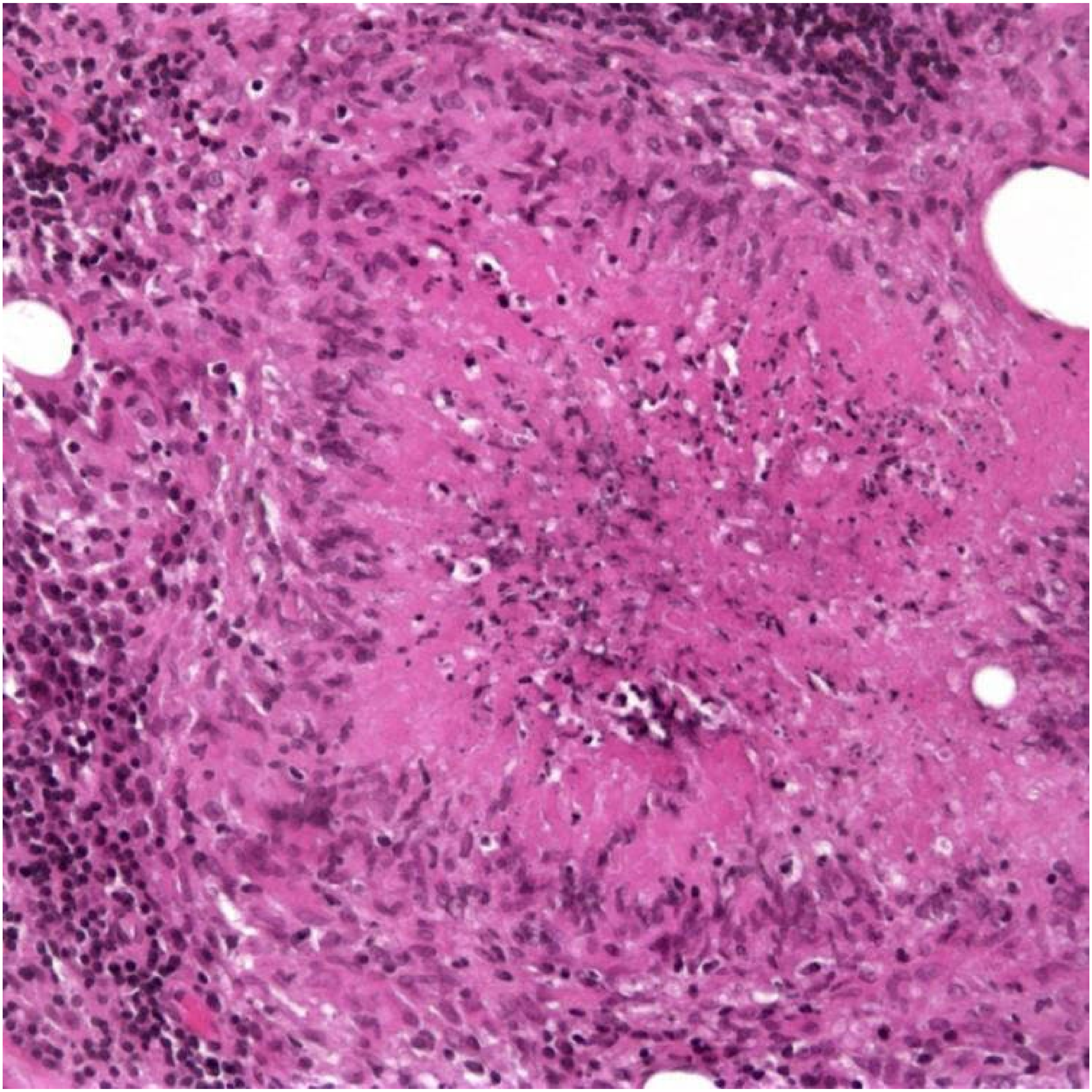
- Culture is more likely to be positive in cases with caseating necrosis
  - May take weeks to grow
- PCR has 53-88% sensitivity and 96-100% specificity

Diagnostic Checklist

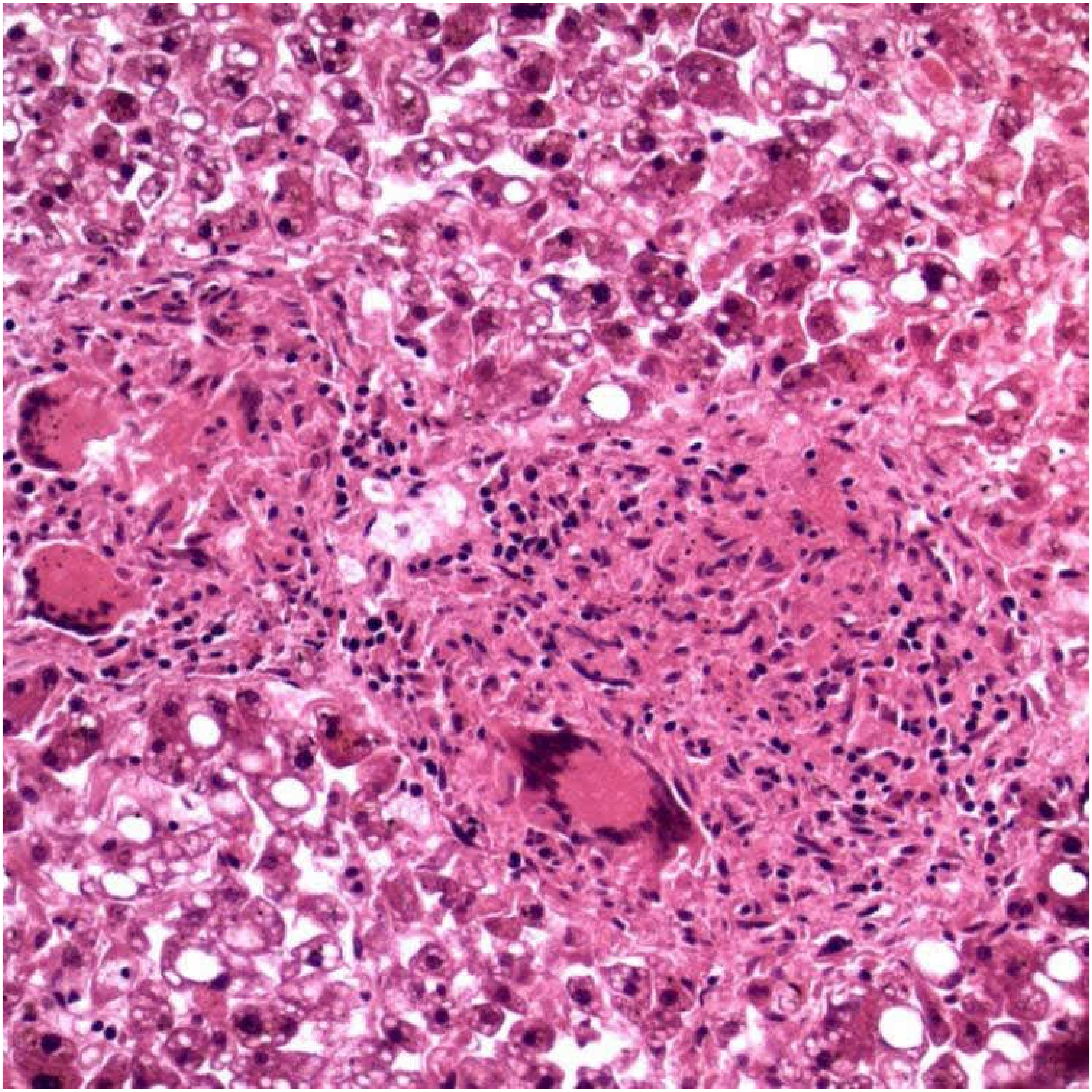
- Have high index of suspicion in patients with hepatomegaly, fever, respiratory symptoms, and elevated liver tests, especially if patient is from endemic area



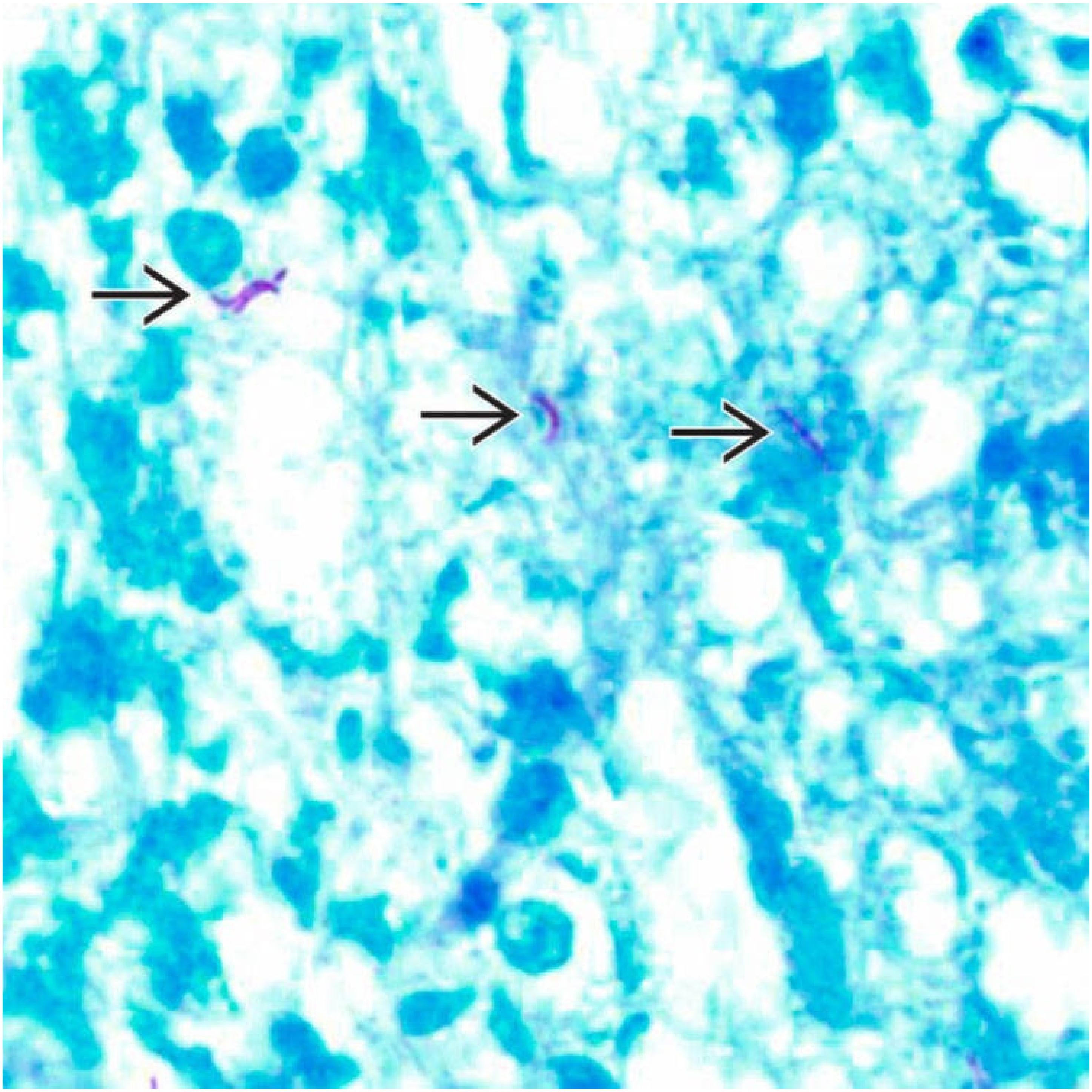
Granuloma With Giant Cells
This liver biopsy in hepatic tuberculosis shows an expansile, portal-based granuloma with associated lymphocytes and giant cells. Note that the granuloma effaces the normal architecture of the liver.



Caseating Necrosis
This patient with disseminated tuberculosis had granulomas with central amorphous granular material, typical of caseating necrosis, within the liver and portal lymph nodes. Note the surrounding palisading histiocytes.



Miliary Tuberculosis in Liver
The liver from an autopsy of a patient with miliary tuberculosis shows a small granuloma with associated lymphocytes and multinucleated giant cells and very focal eosinophilic granular necrotic debris.



AFB Stain
Acid-fast stain shows a few acid-fast bacteria → with a slender, beaded appearance consistent with Mycobacterium tuberculosis.

TERMINOLOGY

Abbreviations

- *Mycobacterium tuberculosis* (MTB)
- Tuberculosis (TB)

Definitions

- Infection by MTB
  - ∼ 8.5 million people develop TB annually; extrapulmonary TB is increasing in frequency
  - – Hepatic TB seen in ∼ 1% of patients with active TB
  - – More common in HIV(+) patients

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Transmission typically by inhalation
  - Can reach liver by hematogenous spread or direct spread from GI tract
  - Widely disseminated disease known as miliary TB

CLINICAL ISSUES

Presentation

- Most common symptoms overall are hepatomegaly, fever, abdominal pain, weight loss
  - Miliary disease
  - More likely to have pulmonary symptoms
- Tuberculoma/localized disease
  - More likely to have abdominal pain
  - Can cause obstructive jaundice from compression of bile ducts
  - Can cause portal hypertension from compression of portal vein
- Tuberculous cholangitis (infection of biliary tree) is rare
  - Presents with biliary strictures and obstructive jaundice
- Elevated alkaline phosphatase most common lab abnormality
  - Transaminases occasionally elevated

Treatment

- Multidrug antituberculous regimens similar to those used to treat TB infecting other sites
  - Drug resistance is increasingly common problem
- May need drainage/excision of localized lesions

Prognosis

- Mortality ranges from 10-40%
  - Risk factors for poor prognosis include age < 20, dissemination, immune-compromising conditions

IMAGING

CT Findings

- Hepatic calcifications in 1/2 of cases

MACROSCOPIC

General Features

- Miliary (~ 80%)
  - Multiple small focal lesions, often not grossly visible
- Mass lesions (tuberculoma)
  - Cheesy or chalky white, irregular nodules

MICROSCOPIC

Histologic Features

- Numerous granulomas with central amorphous granular necrotic debris (caseating necrosis)
  - Immunocompromised patients often have poorly formed granulomas or collections of foamy histiocytes with innumerable organisms
  - Variably present lymphocytes, giant cells
- Some cases have more loosely formed lymphohistiocytic lesions without necrosis
- Tuberculomas may result from numerous confluent granulomas
- Acid-fast stains (+) in up to 60% of cases
  - Cell wall rich in lipomannan, lipoarabinomannan, and mycolic acid is responsible for acid-fast staining

ANCILLARY TESTS

Culture

- More likely to be positive in cases with caseating necrosis

PCR

- Sensitivity of 53-88% and specificity of 96-100%

DIFFERENTIAL DIAGNOSIS

Sarcoidosis

- Typically nonnecrotizing; negative for organisms

Neoplasm

- Tuberculoma may mimic neoplasm both clinically and radiographically

Fungal Infection

- GMS stain, fungal culture

Bacterial Infection

- Culture, histochemical stain, PCR

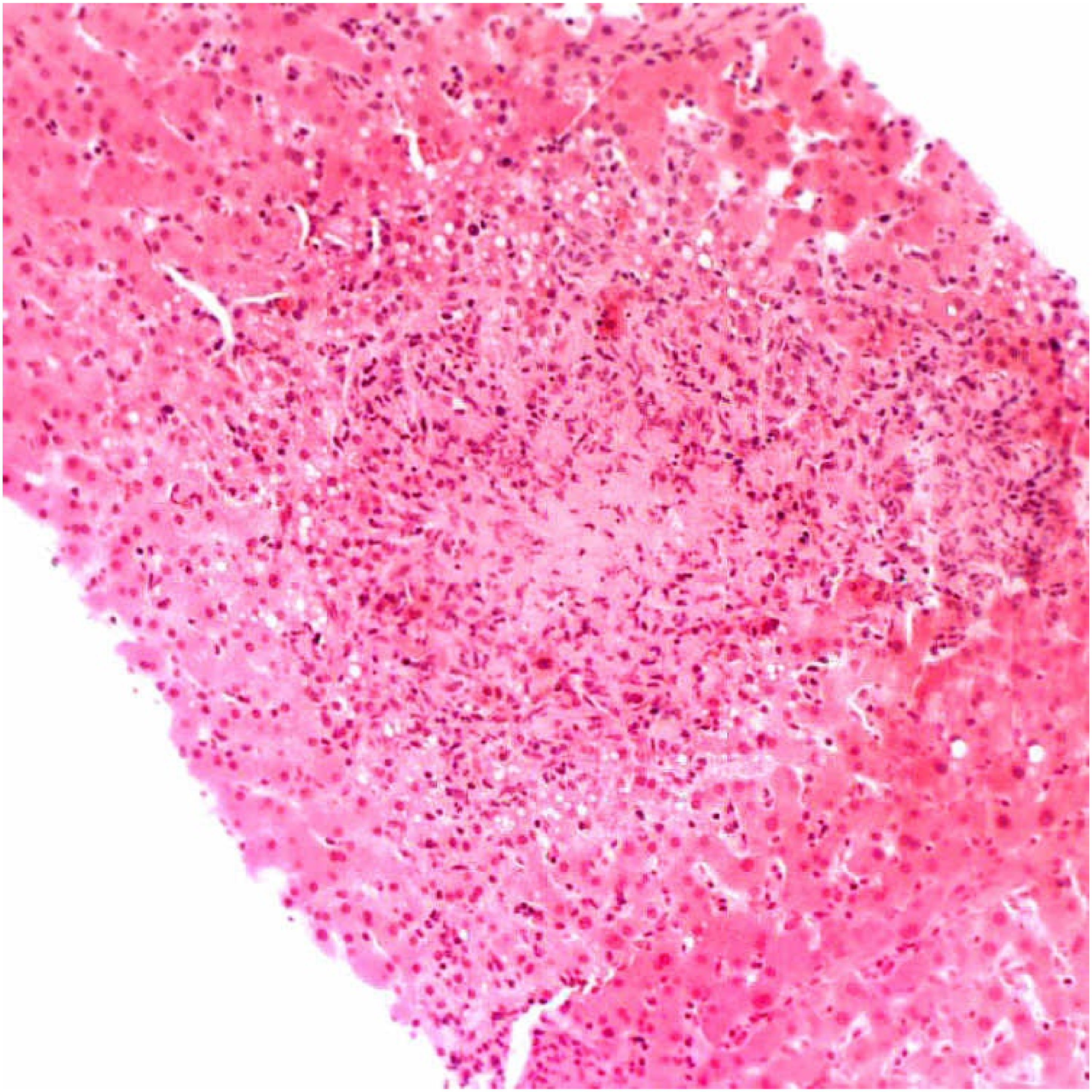
Other Mycobacterial Species

- Leprosy, atypical mycobacteria can look similar
- Clinical features, culture, PCR

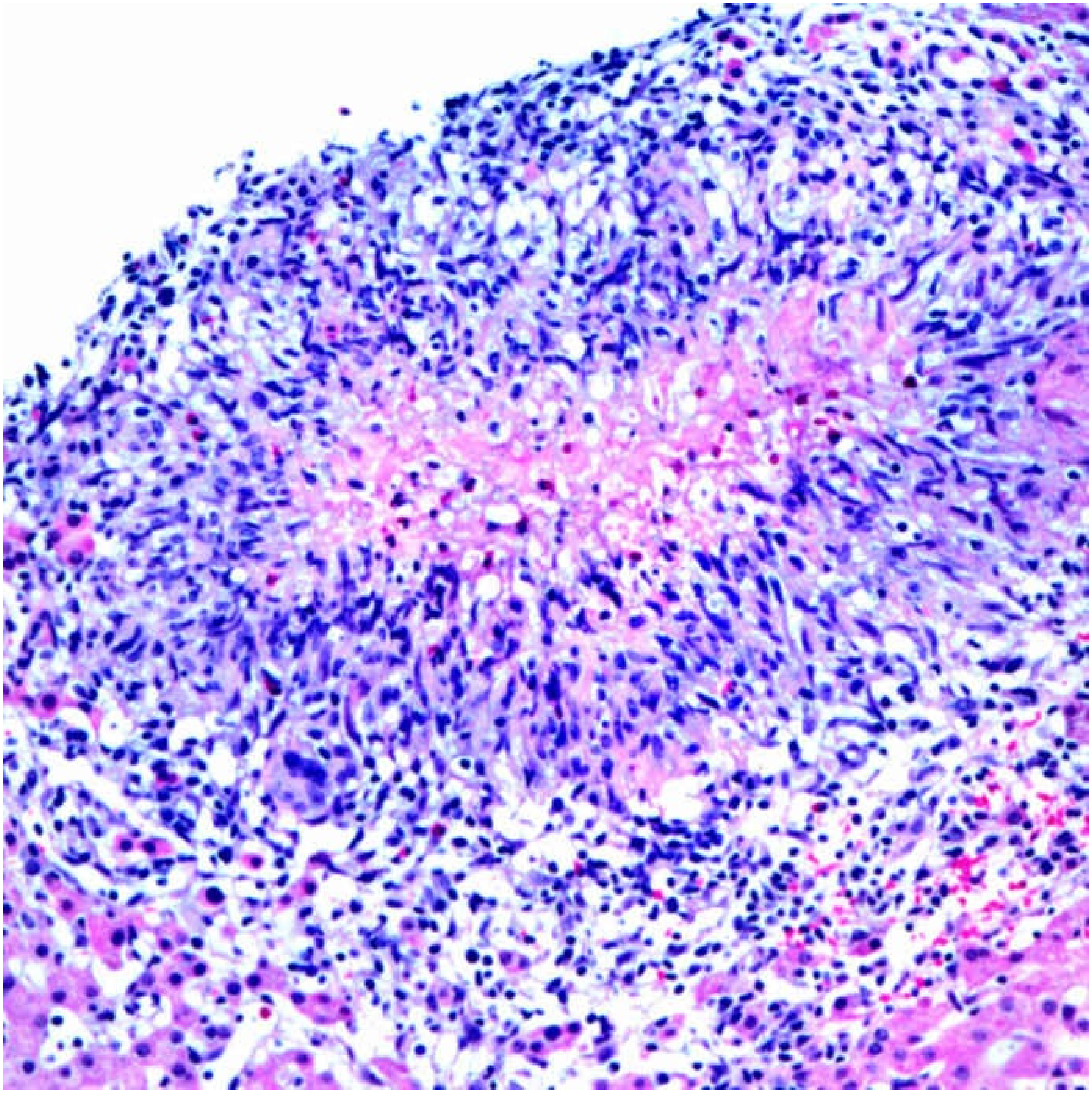
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

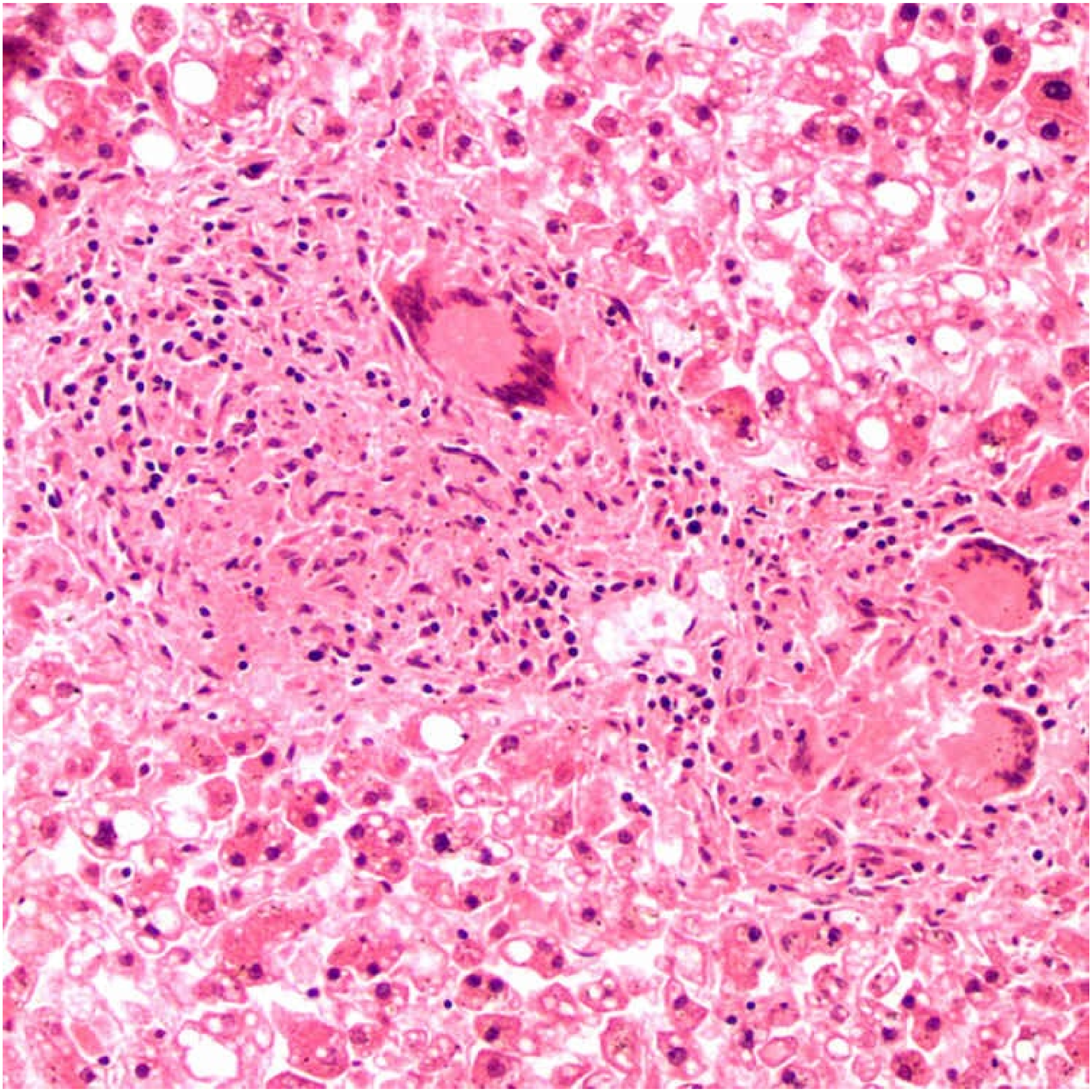
- High index of suspicion in patients with hepatomegaly, fever, respiratory symptoms, and elevated liver tests, especially if patient is from endemic area

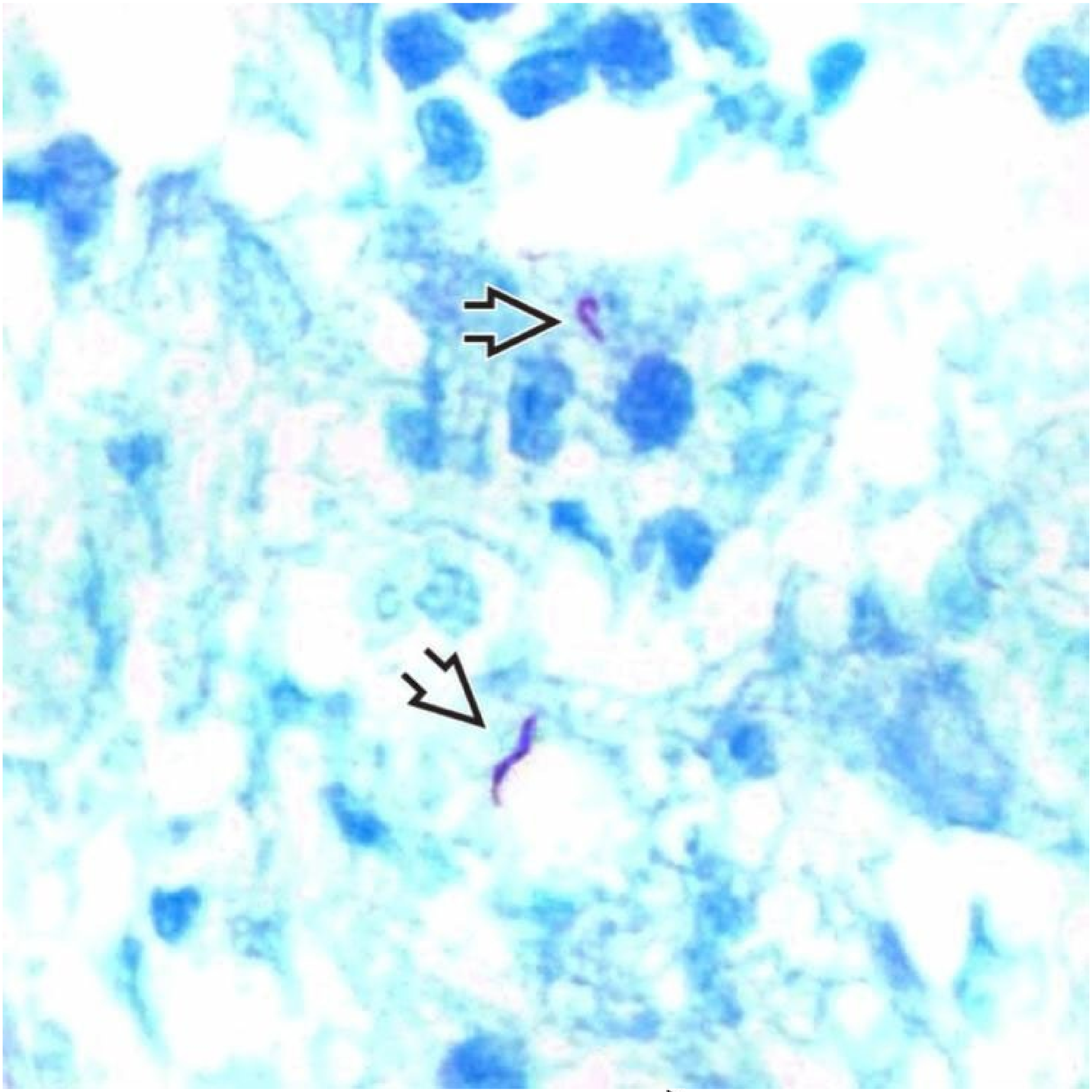


Liver biopsy in hepatic tuberculosis shows an expansile granuloma with central caseating necrosis.

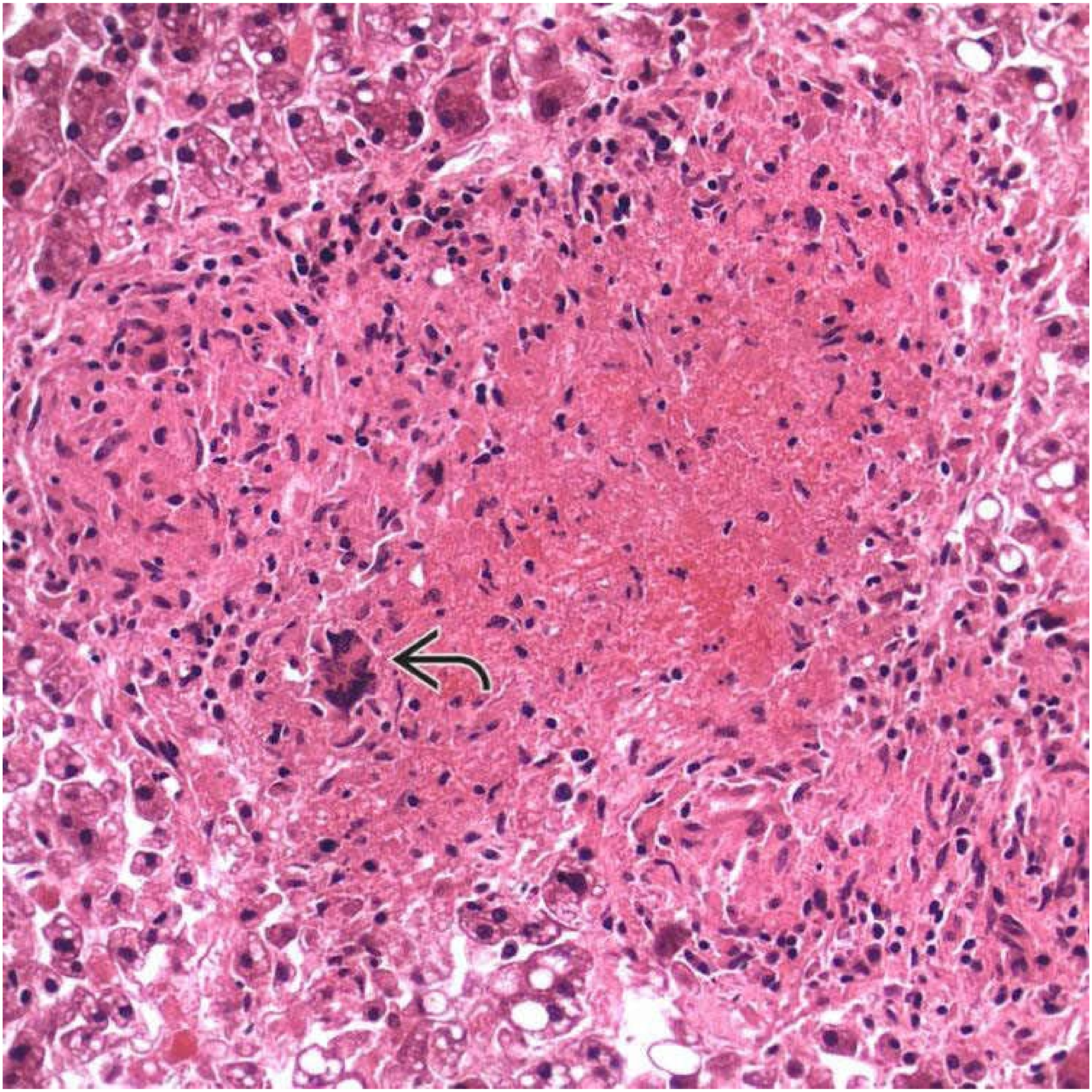


A necrotizing granuloma features central necrosis surrounded by a rim of palisading histiocytes and lymphocytes.

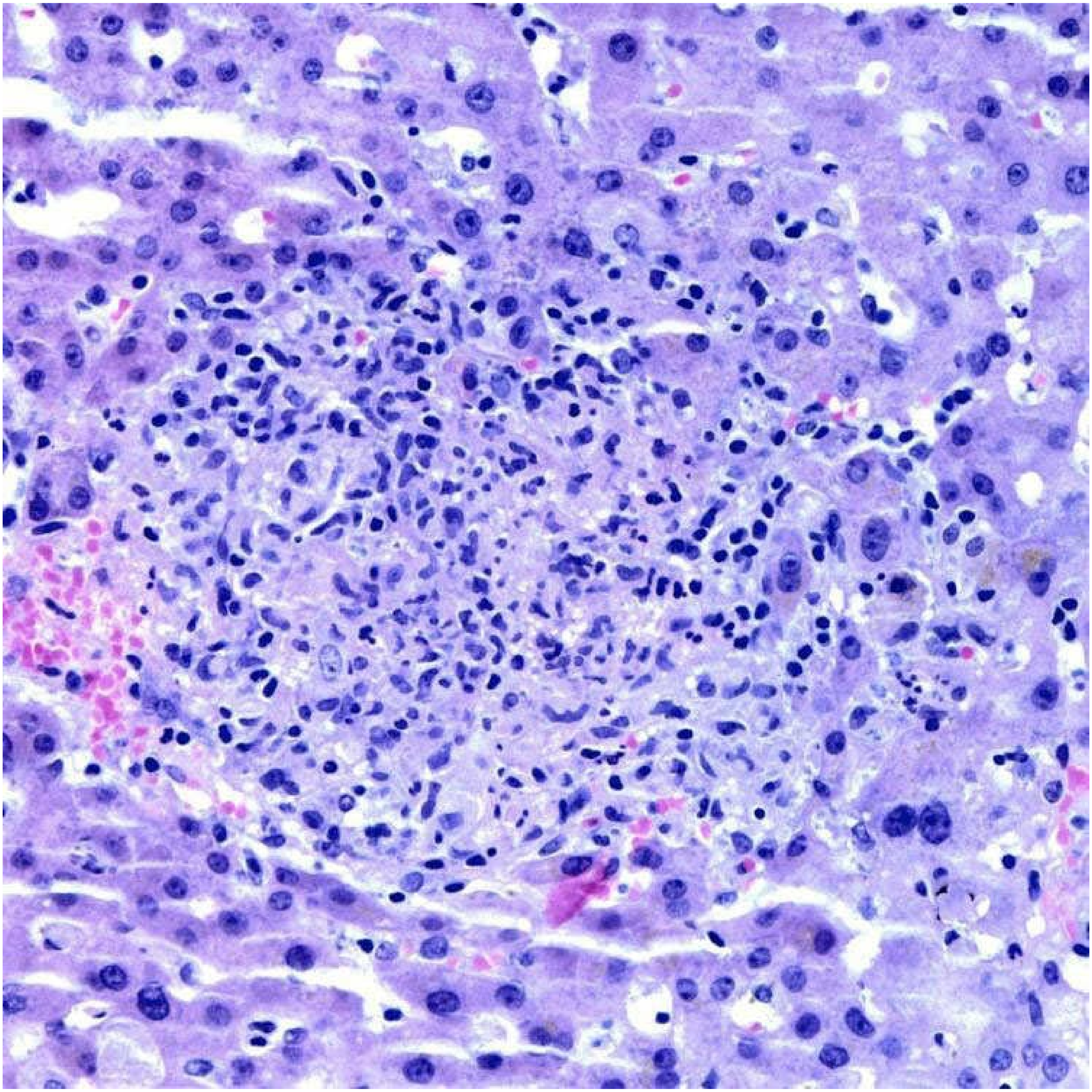

High-power view of hepatic miliary tuberculosis shows a granuloma with focal eosinophilic granular necrotic material and several multinucleated giant cells.



An AFB stain shows rare slender, beaded acid-fast bacteria ➪ consistent with M. tuberculosis.



High-power view of hepatic tuberculosis shows a caseating granuloma characterized by central eosinophilic granular material, with surrounding histiocytes and a multinucleated giant cell .



This liver biopsy is from a patient with tuberculosis and liver and spleen lesions. The granuloma consists of a mixture of histiocytes and lymphocytes, but there is no significant necrosis.

SELECTED REFERENCES

1. Hickey, AJ, et al. A systematic review of hepatic tuberculosis with considerations in human immunodeficiency virus co-infection. *BMC Infect Dis*. 2015; 15:209.
2. Mourad, MM, et al. Primary hepatic tuberculosis in immunocompetent adults: a UK case series. *Oxf Med Case Reports*. 2014; 2014(9):148–150.
3. Chong, VH. Hepatobiliary tuberculosis: a review of presentations and outcomes. *South Med J*. 2008; 101(4):356–361.
4. Wang, JY, et al. Disseminated tuberculosis: a 10-year experience in a medical center. *Medicine (Baltimore)*. 2007; 86(1):39–46.

5. Maharaj, B, et al. A prospective study of hepatic tuberculosis in 41 black patients. *Q J Med*. 1987; 63(242):517–522.
6. Essop, AR, et al. Tuberculosis hepatitis: a clinical review of 96 cases. *Q J Med*. 1984; 53(212):465–477.

Atypical Mycobacteria

KEY FACTS

Terminology

- Infection by mycobacteria other than tuberculosis or leprosy
  - Numerous species widely present in environment; worldwide distribution
  - – Transmission typically by inhalation or ingestion
- *Mycobacterium avium* and *Mycobacterium intracellulare*, known together as *Mycobacterium avium-intracellulare* complex (MAC), most commonly cause hepatic disease

Clinical Issues

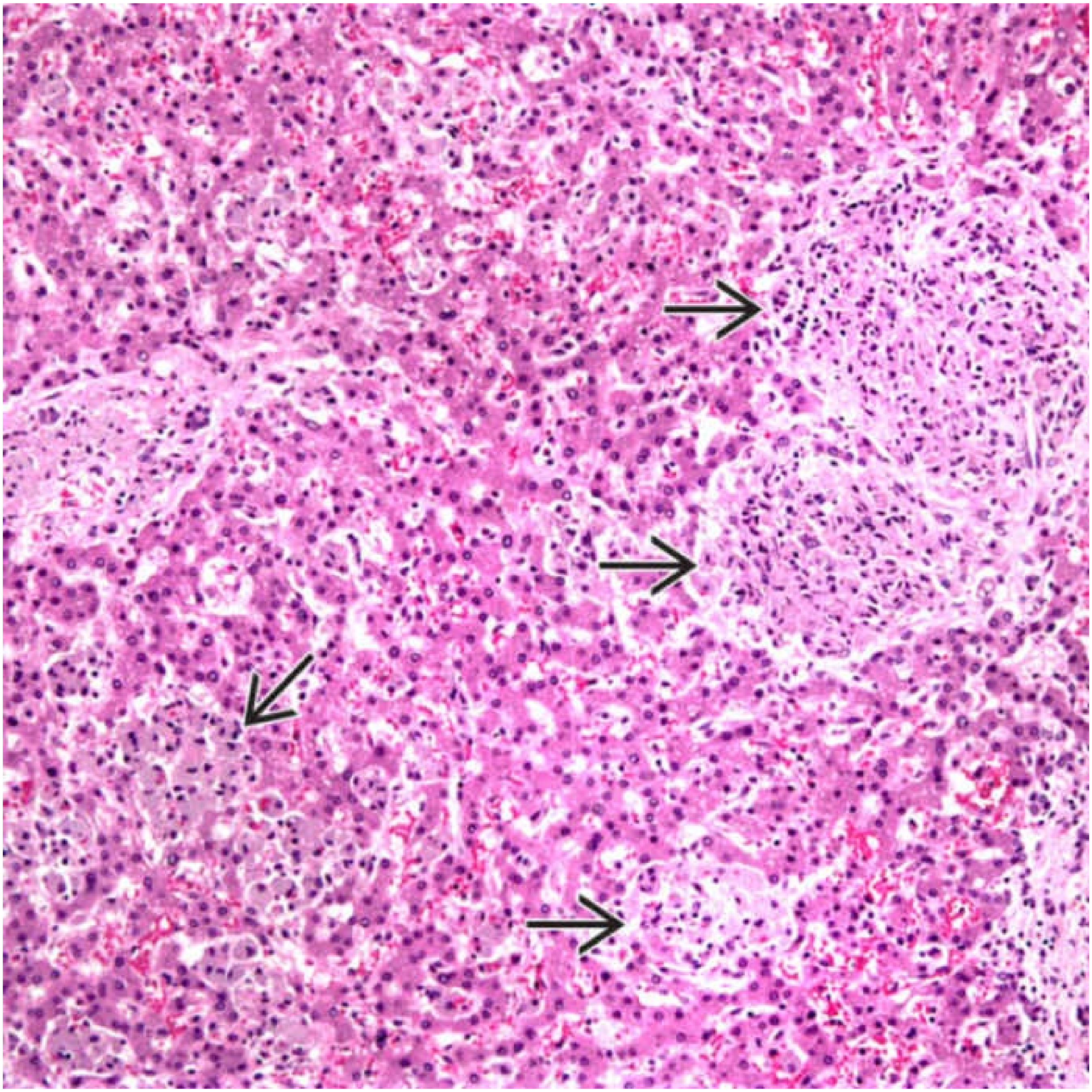
- Common opportunistic infection in AIDS patients, particularly those that have CD4 counts < 50 cells/μL
  - Up to 35% of all AIDS patients develop disseminated MAC eventually
- Helpful laboratory tests include mycobacterial blood culture and PCR
- Treatment is multidrug regimen for many months
  - Drug resistance is problematic
  - Prognosis generally poor

Microscopic

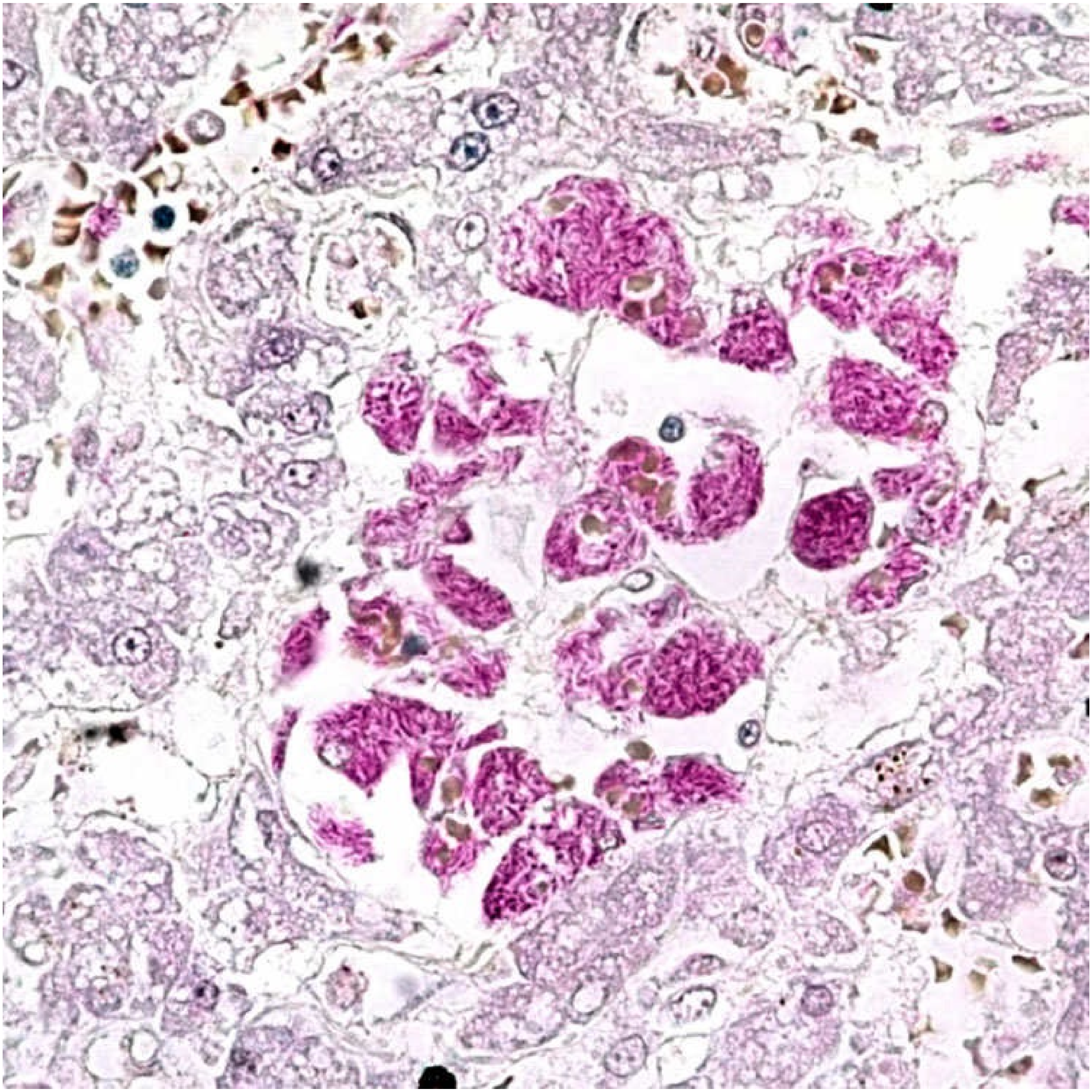
- Wide range of histologic features depending on immune status of patient with numerous acid-fast organisms on acid-fast bacterial stain
  - Poorly formed granulomas, loose aggregates of histiocytes, or of foamy histiocytes
  - Fibrin ring granulomas
  - Necrosis/abscess
  - Spindle cell pseudotumor
- AFB stains often show large numbers of organisms in immunocompromised patients
- In patients with preserved T-cell function, granulomas can be well formed, similar to tuberculosis

Diagnostic Checklist

• Aggregates of foamy histiocytes in liver biopsy from patient with AIDS warrants stains for acid-fast bacteria

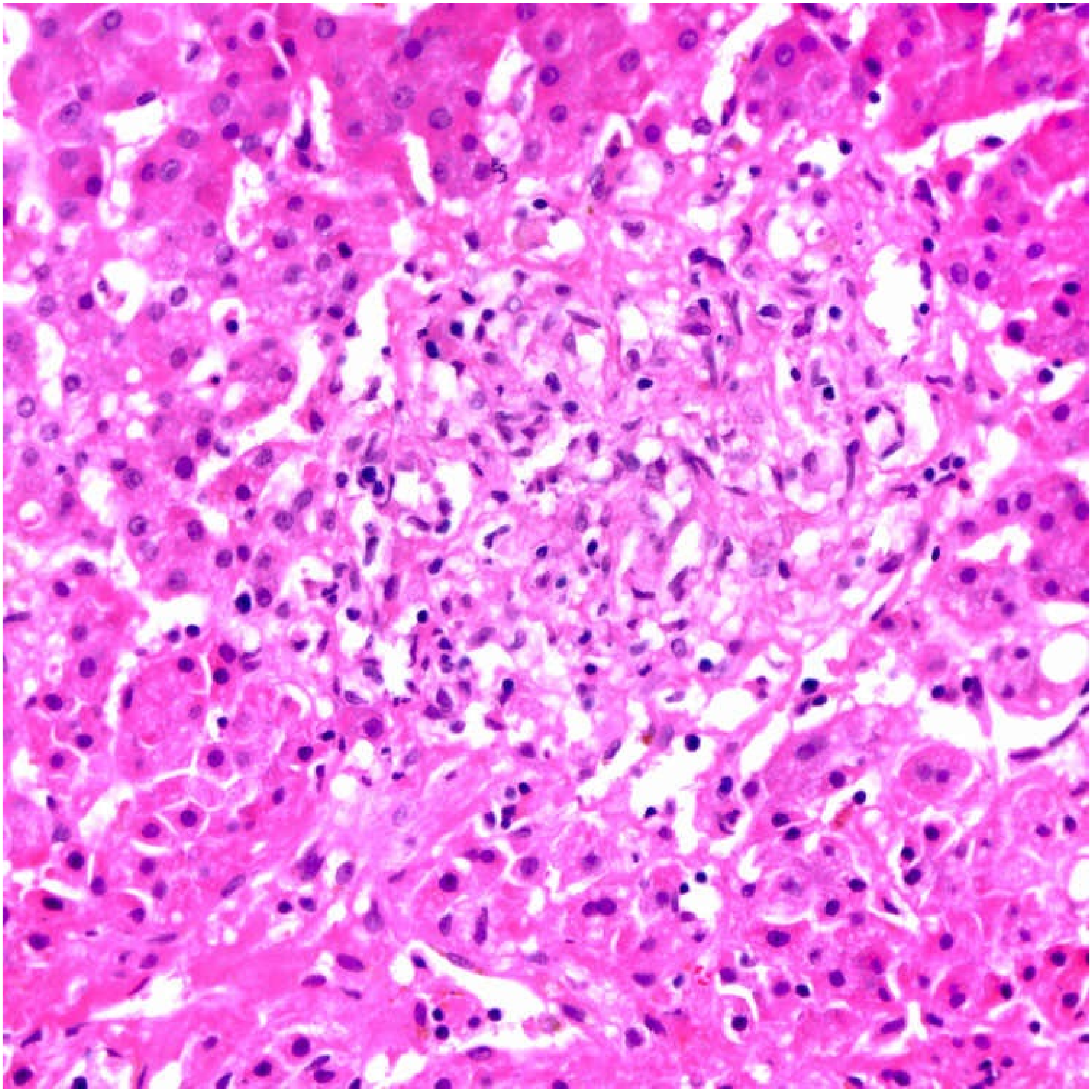


Aggregates of Foamy Histiocytes
This liver from an AIDS patient who died of a Mycobacterium avium-intracellulare complex (MAC) infection shows loose aggregates of foamy histiocytes and poorly formed granulomas → with minimal inflammation in the lobule or associated with the granulomas.

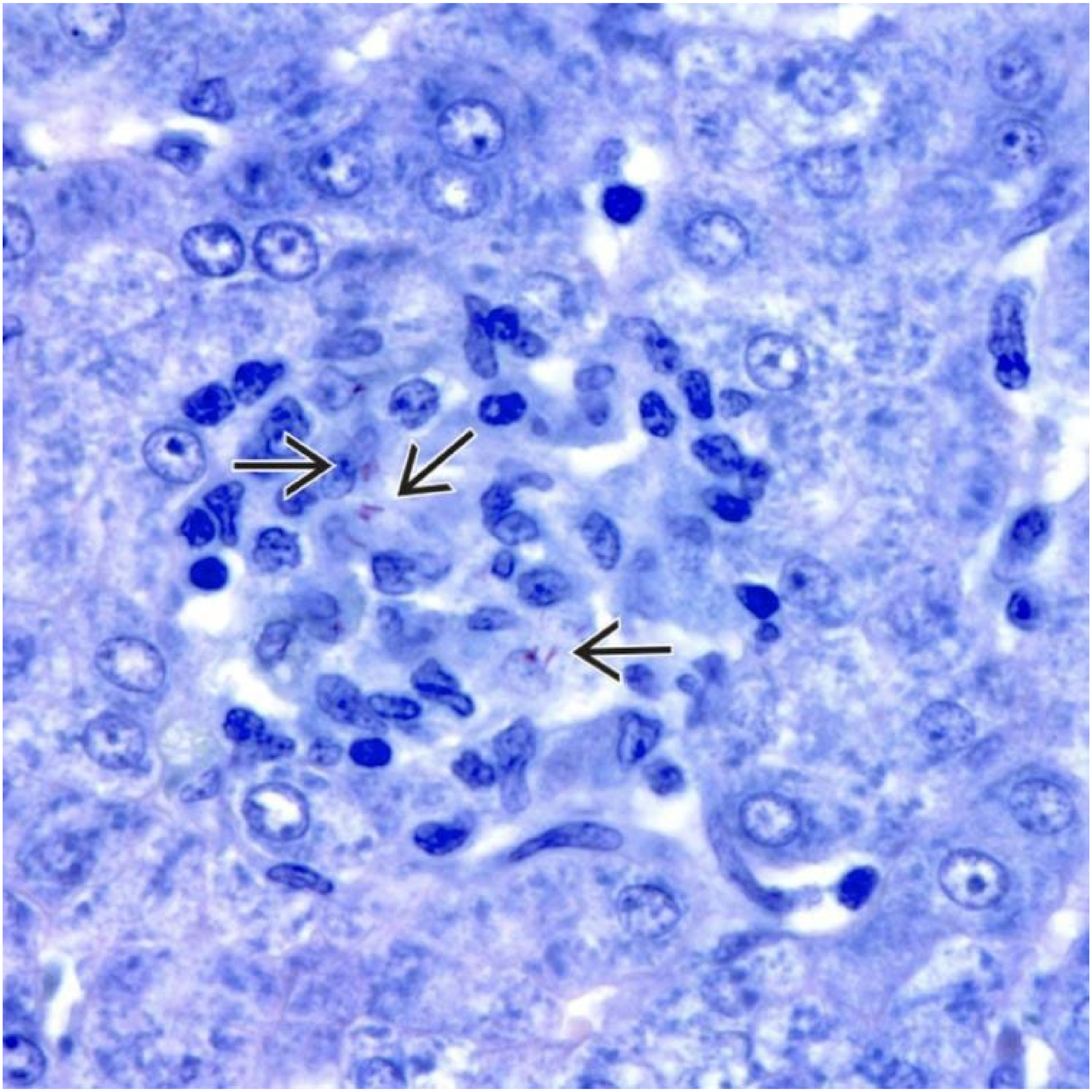


Numerous Organisms on AFB Stain

Ziehl-Neelsen stain shows innumerable acid-fast bacteria within clustered histiocytes in a patient with MAC infection of the liver.



Poorly Formed Granuloma
This high-power view of a poorly formed granuloma in a MAC infection shows a rounded, loose collection of histiocytes.



Scattered Organisms on AFB Stain
Scattered acid-fast rods → are seen on this AFB stain. Immunocompetent patients often have fewer lesional organisms than immunocompromised patients.

TERMINOLOGY

Abbreviations

- *Mycobacterium avium-intracellulare* complex (MAC)

Definitions

- Infection by any one of many species of nontubercular mycobacteria

- Classified according to growth rate, presence, or absence and type of pigment
- Includes *M avium*, *M. intracellulare*, *M. kansasii*, *M. marinum*, *M. gordonae*, *M. chelonae*, *M. scrofulaceum*, *M. szulgai*, *M. malmoense*, *M. xenopi*, *M. abscessus*, and *M. fortuitum*

ETIOLOGY/PATHOGENESIS

Infectious Agents

- Numerous species widely present in environment; worldwide distribution
  - Transmission typically by inhalation or ingestion
  - *Mycobacterium avium* and *Mycobacterium intracellulare*, known together as MAC, most commonly cause hepatic disease
  - Next to MAC, *Mycobacterium kansasii* is most common cause of nontuberculous mycobacterial infection in HIV patients

CLINICAL ISSUES

Epidemiology

- Incidence
  - Up to 35% of all AIDS patients develop disseminated MAC eventually
  - 1-year incidence is 3% among patients with CD4 counts between 100-199 cells/μL and 39% for patients with CD4 counts < 10 cells/μL
  - Frequency is decreasing with widespread use of highly active antiretroviral therapy (HAART)
- Sex
  - More common in males, mirroring HIV prevalence
- Risk factors
  - AIDS, malignancy, chronic renal disease, chronic pulmonary disease, cystic fibrosis, and alcoholism
    - In AIDS patients with MAC, CD4 counts are usually < 50 cells/μL

Presentation

- Fever, hepatomegaly, elevated alkaline phosphatase
  - Patients treated with HAART may develop clinical manifestations of disseminated MAC due to immune reconstitution syndrome
  - MAC most common pathogen associated with immune reconstitution syndrome

Laboratory Tests

- Mycobacterial blood culture
  - Slow growing (2-3 weeks for MAC)
- Molecular identification
  - Can be performed of fresh or routinely processed tissue
  - Can distinguish *Mycobacterium tuberculosis* from nontubercular species

Treatment

- Drugs
  - Multidrug regimen for many months

Prognosis

- Median survival: 6 months, with only 24% of patients surviving for 1 year
  - Poor survival is often function of advanced AIDS rather than disseminated MAC infection

IMAGING

CT Findings

- Hepatomegaly, uniform attenuation of lymph nodes, and clustered pattern of lymph nodes

MICROSCOPIC

Histologic Features

- Wide range of histologic features depending on immune status of patient
  - Poorly formed granulomas, aggregates of histiocytes or foamy histiocytes common in immunosuppressed patients
    - Typically minimal attendant inflammation
    - Fibrin ring granulomas have been described
  - Necrotic areas filled with inflammatory cells and nuclear debris or liver abscess may be seen
- Spindled histiocytes forming mass lesion may be seen in immunocompromised patients as well (mycobacterial spindle cell pseudotumor)
- In patients with preserved T-cell function, granulomas can be well formed, similar to tuberculosis
- Acid-fast bacterial stains (Ziehl-Neelsen, Kinyoun, Fite stains)
  - Immunocompromised patients typically have numerous acid-fast organisms in macrophages
  - Organisms may be extremely rare in immune competent patients

DIFFERENTIAL DIAGNOSIS

Tuberculosis

- Granulomas typically well formed with caseating necrosis and fewer organisms
- Clinical setting, culture, PCR are helpful

Histoplasmosis

- Can also cause aggregates of foamy histiocytes in immunocompromised patients
  - GMS stain demonstrates yeast in histiocytes
  - Caveat: GMS stain will also stain rapidly dividing atypical mycobacteria

- Fungal culture, PCR helpful

Q Fever

- Prototypical disease associated with fibrin ring granulomas
- Rickettsial disease that usually manifests as pneumonitis or endocarditis
- Serologies for *Coxiella burnetii* may be helpful but may be false-negative in severely immunocompromised patients

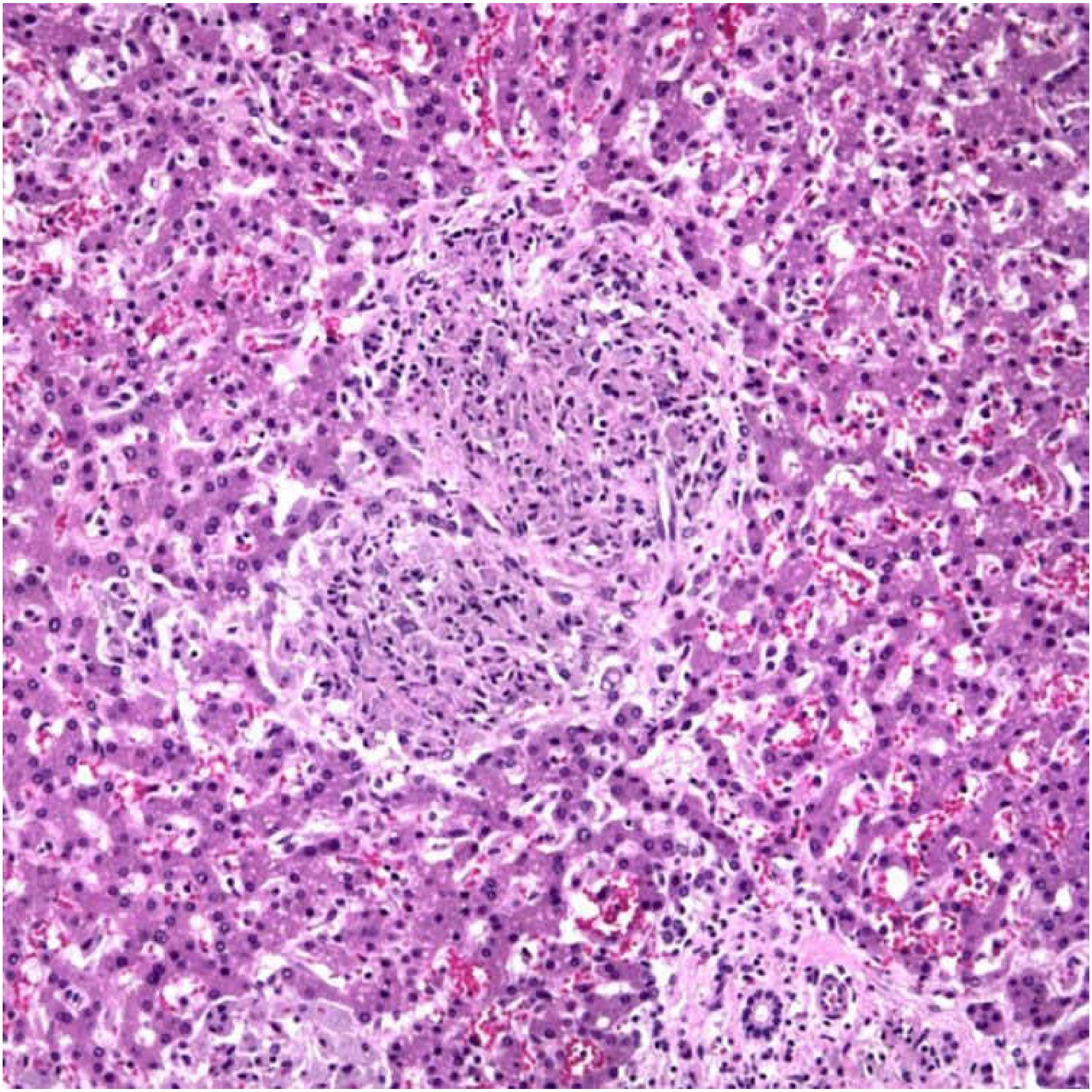
Leprosy

- Lepromatous leprosy shows aggregates of foamy histiocytes
- Clinical setting, culture, PCR are helpful

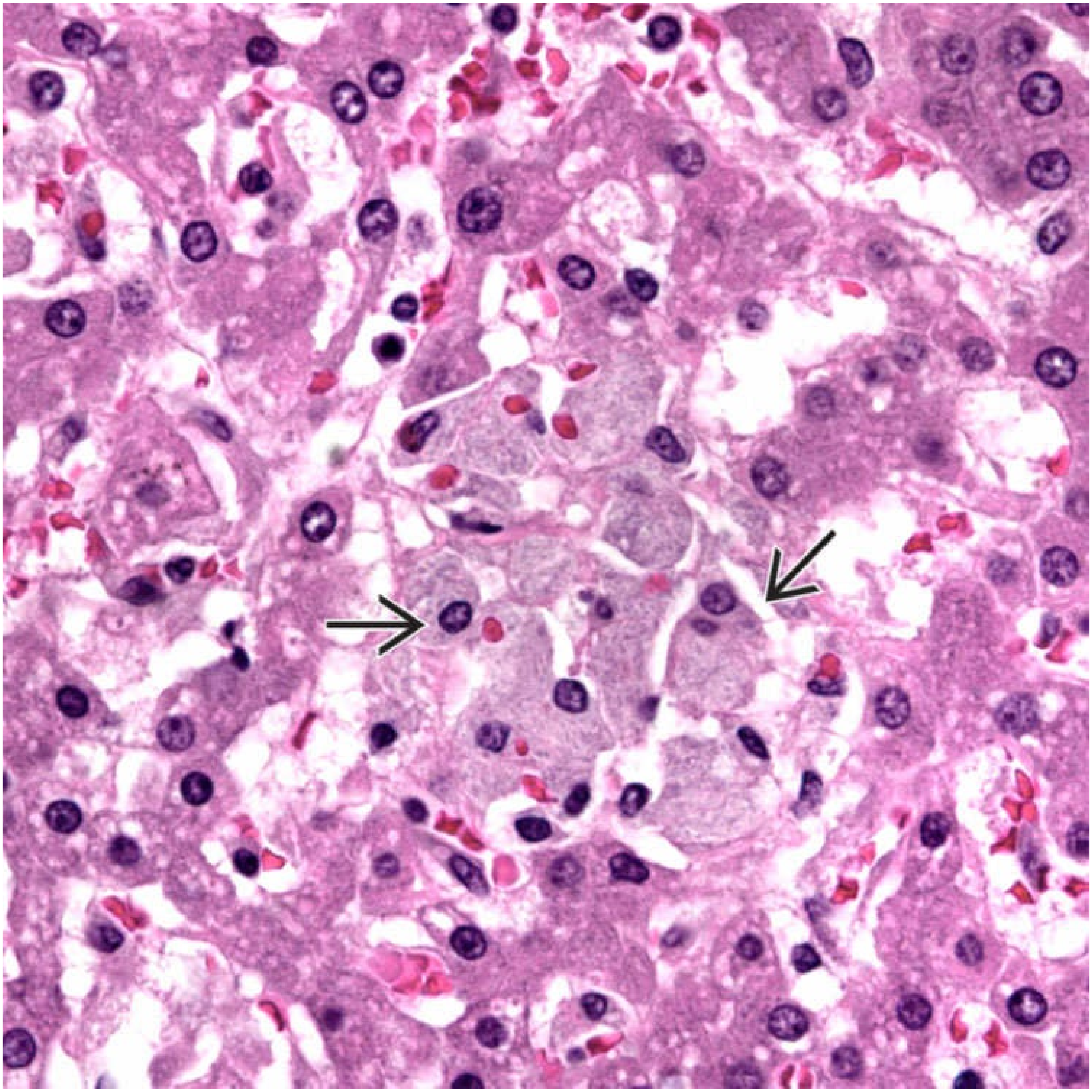
DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

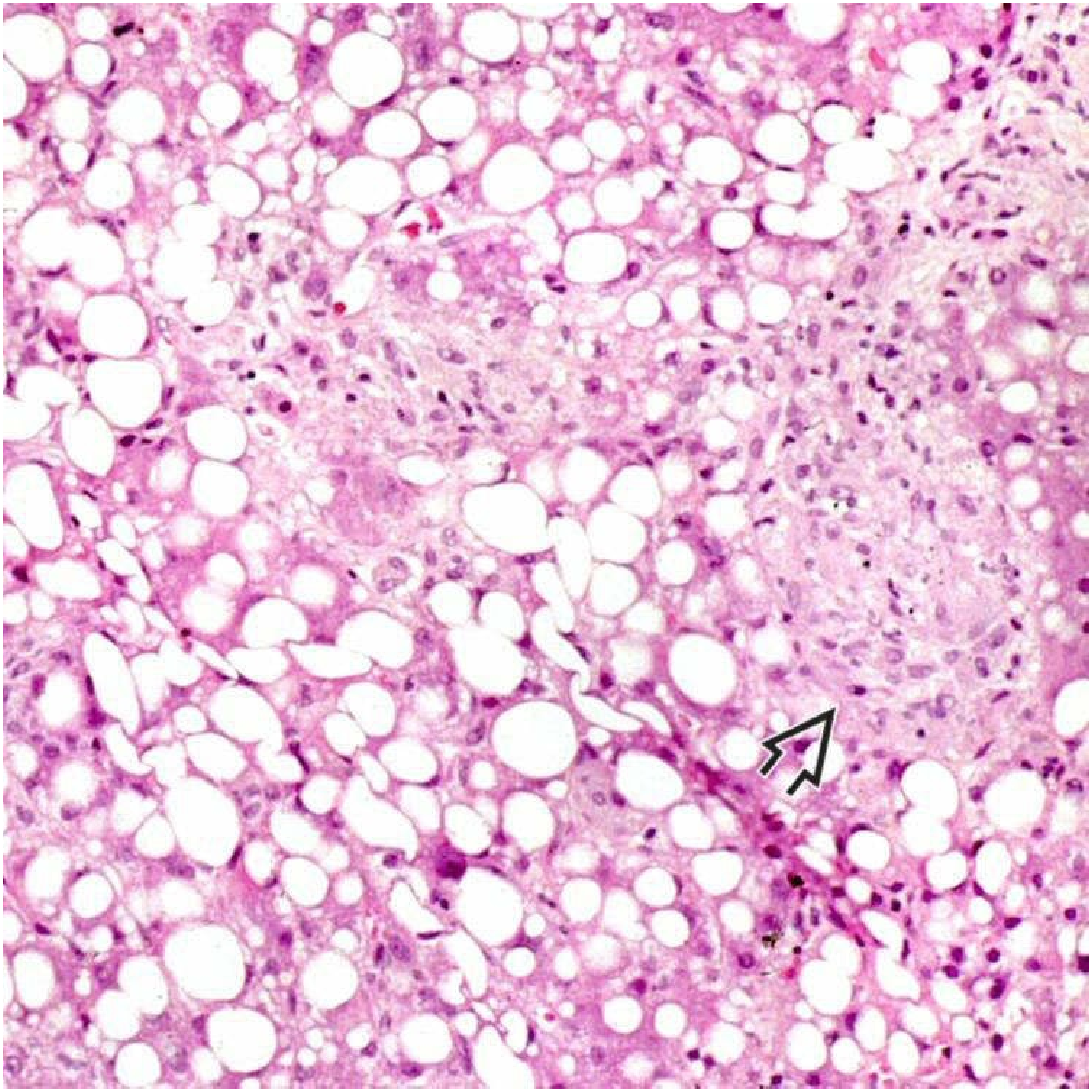
- Aggregates of foamy histiocytes in liver biopsy from patient with AIDS warrants stains for acid-fast organisms



Foamy Histiocyte Aggregates
This autopsy specimen from a patient who died of a MAC infection shows a large aggregate of foamy histiocytes forming a loose granuloma that is centered on a portal tract. There is minimal associated inflammation as the patient was HIV(+) and severely immune compromised.

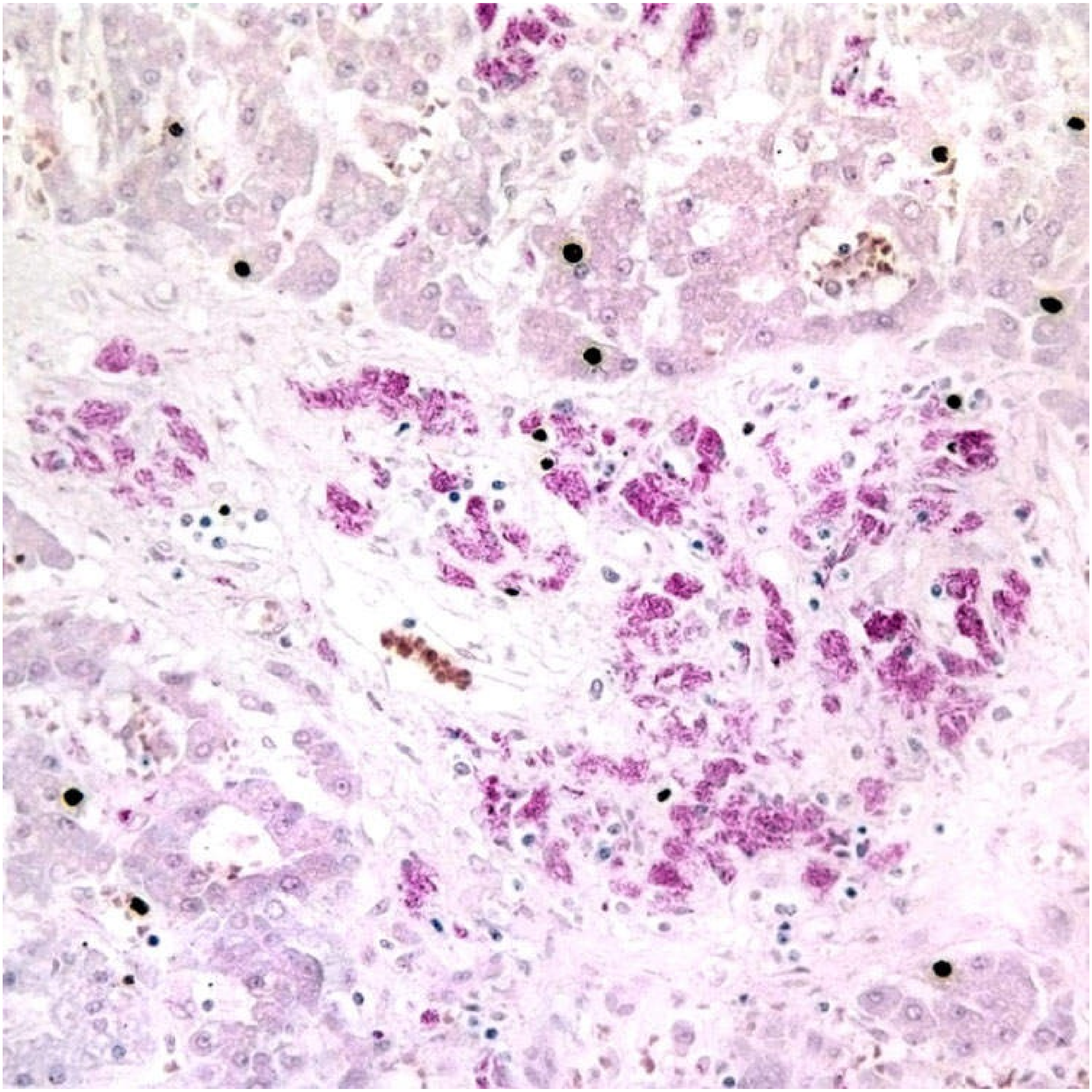


Foamy Histiocyte Aggregate
An aggregate of foamy histiocytes → is shown in the hepatic lobule in a patient with a MAC infection. There is virtually no associated inflammation.

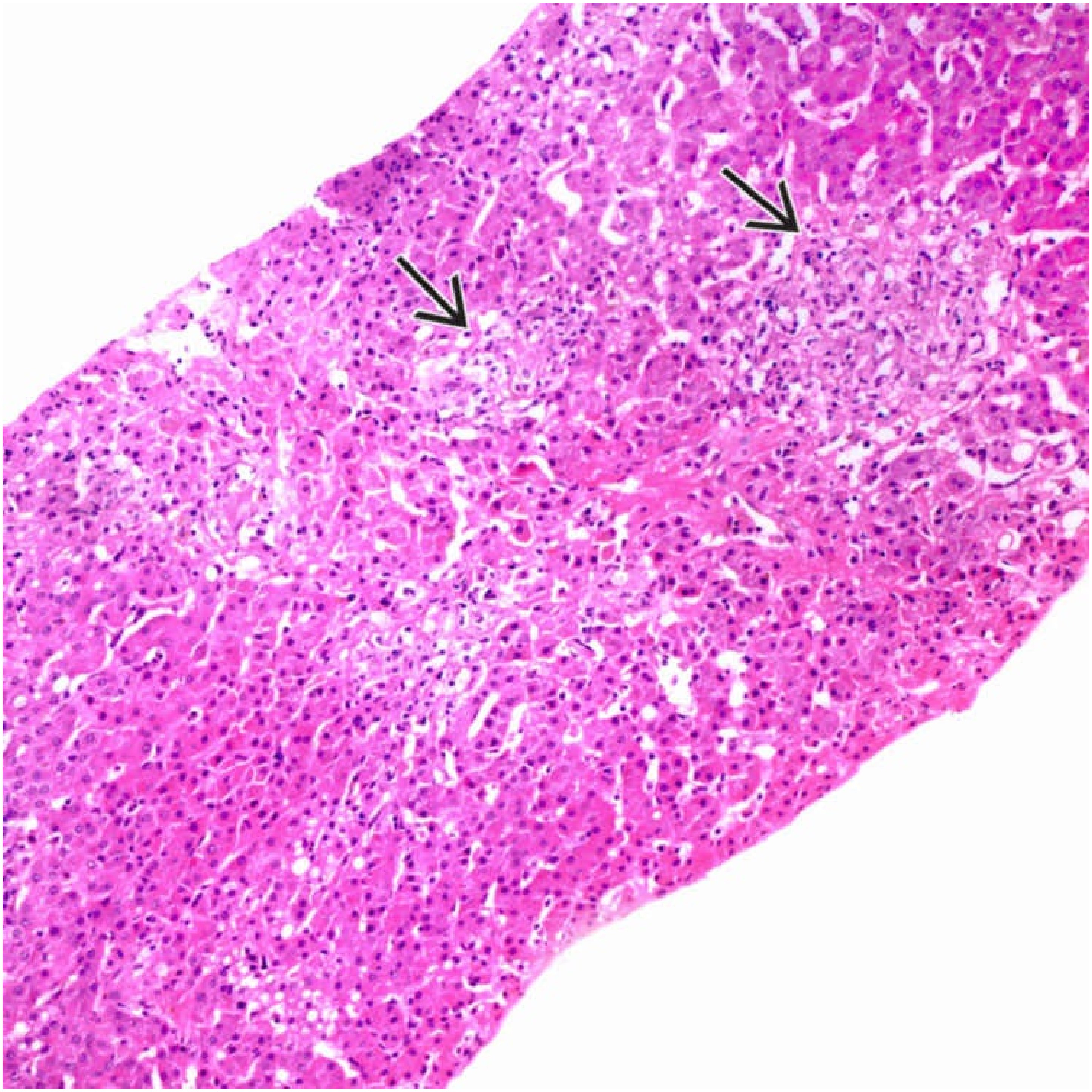


Loosely Formed Granulomas

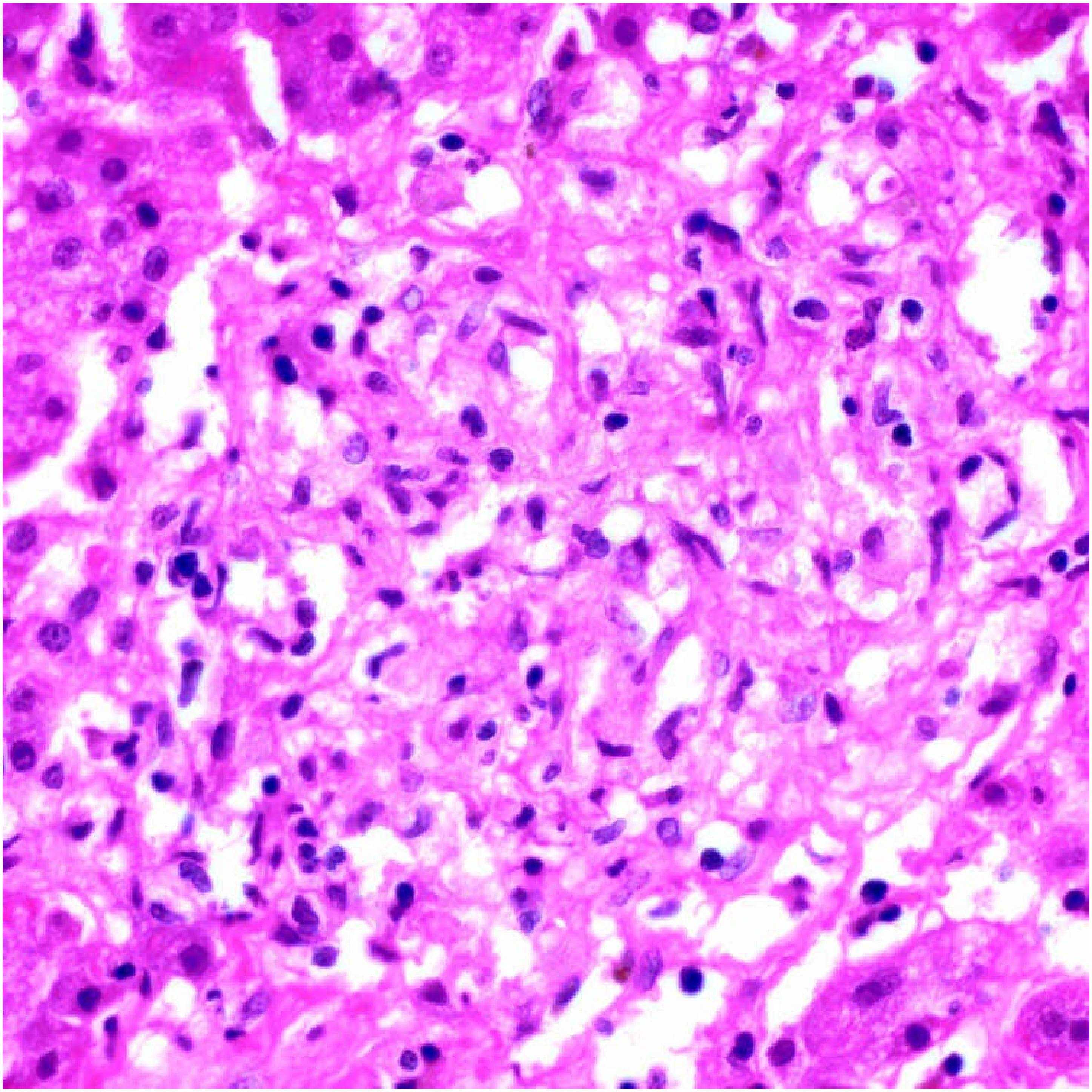
Loosely formed, noncaseating granulomas ➩ are present throughout the liver in a patient with a disseminated MAC infection.



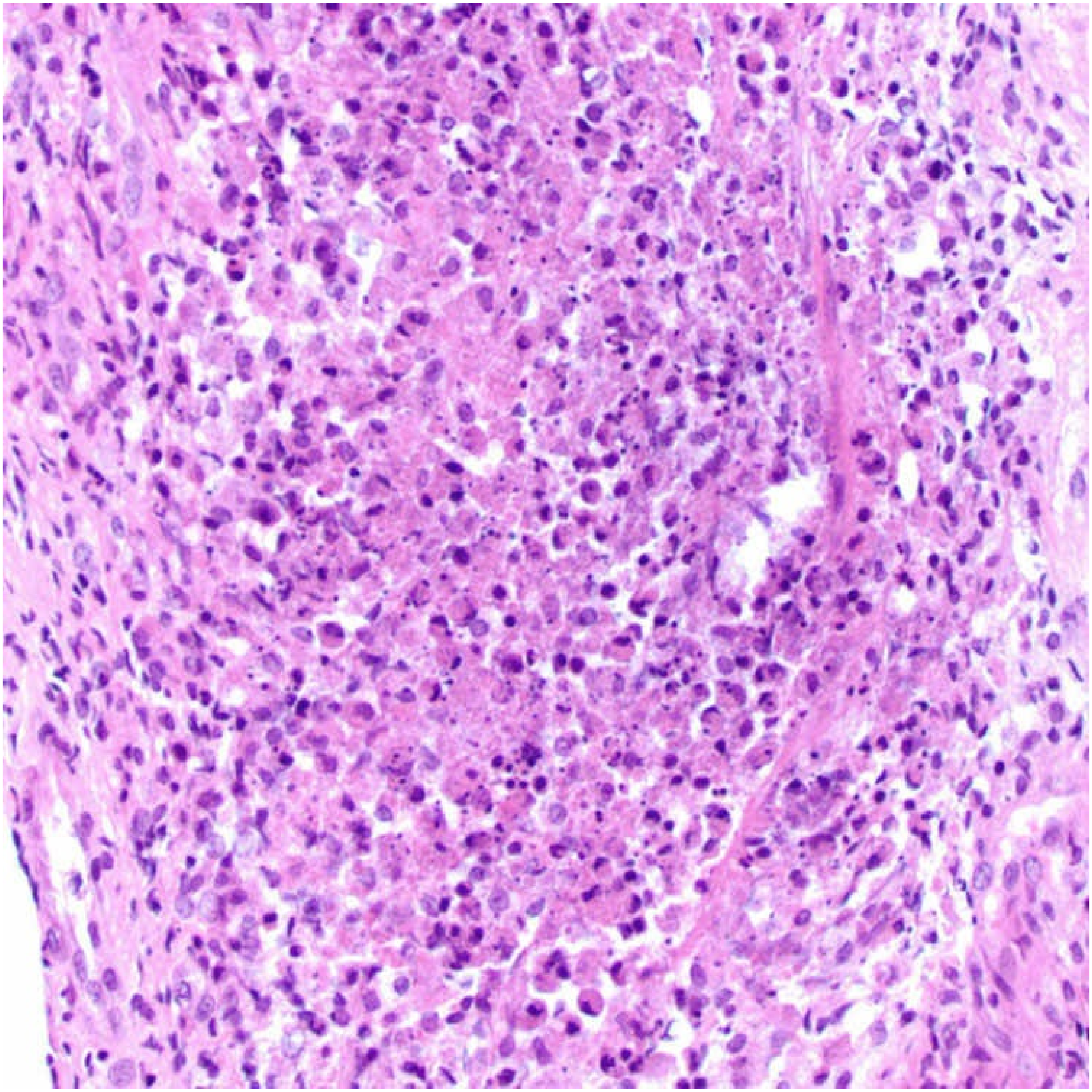
Portal Macrophages on AFB Stain
An acid-fast stain shows numerous acid-fast bacilli within portal macrophages in an immunocompromised patient with a MAC infection.



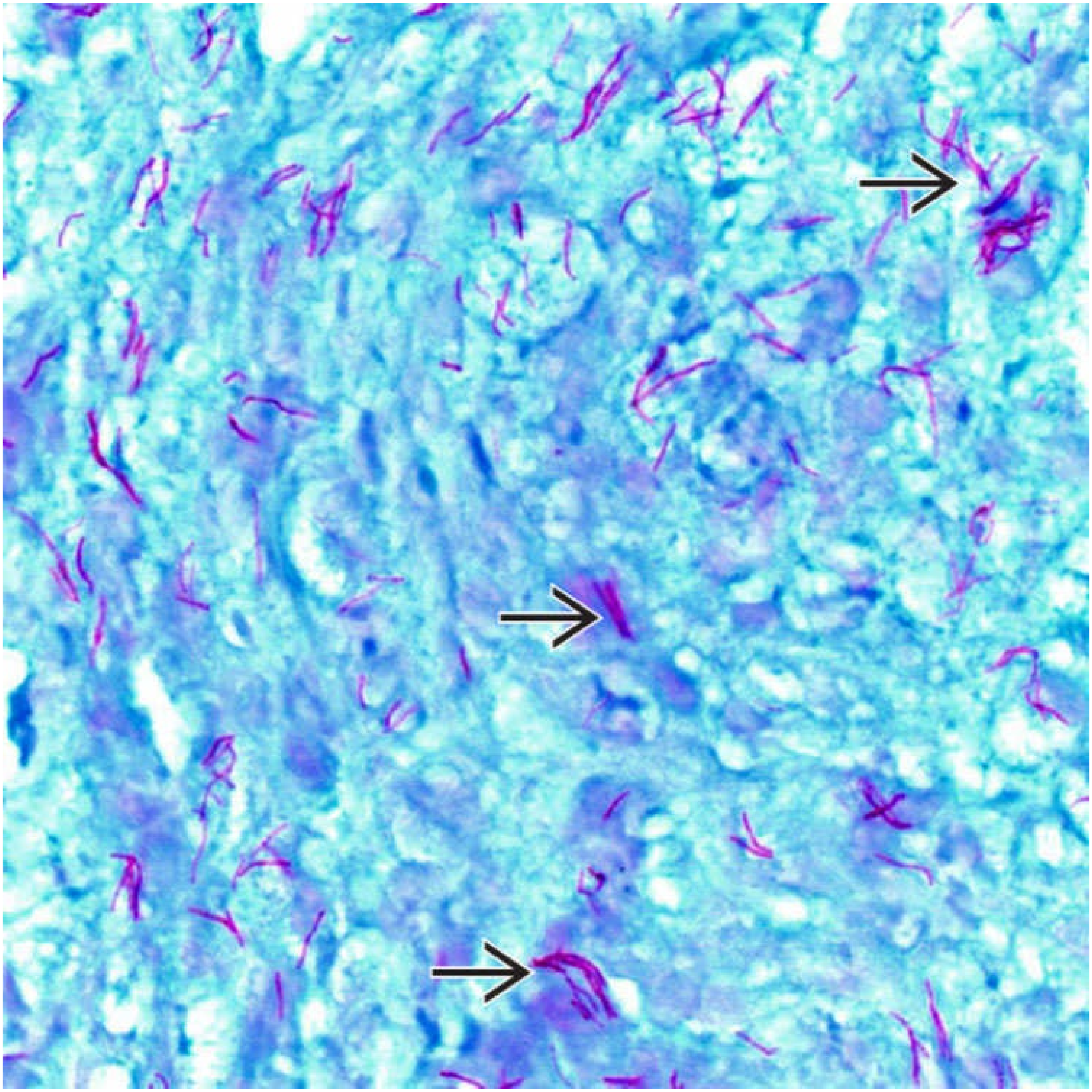
Multiple Poorly Formed Granulomas
This low-power view of a liver biopsy in a patient with a MAC infection shows poorly formed granulomas →
throughout the needle core biopsy.



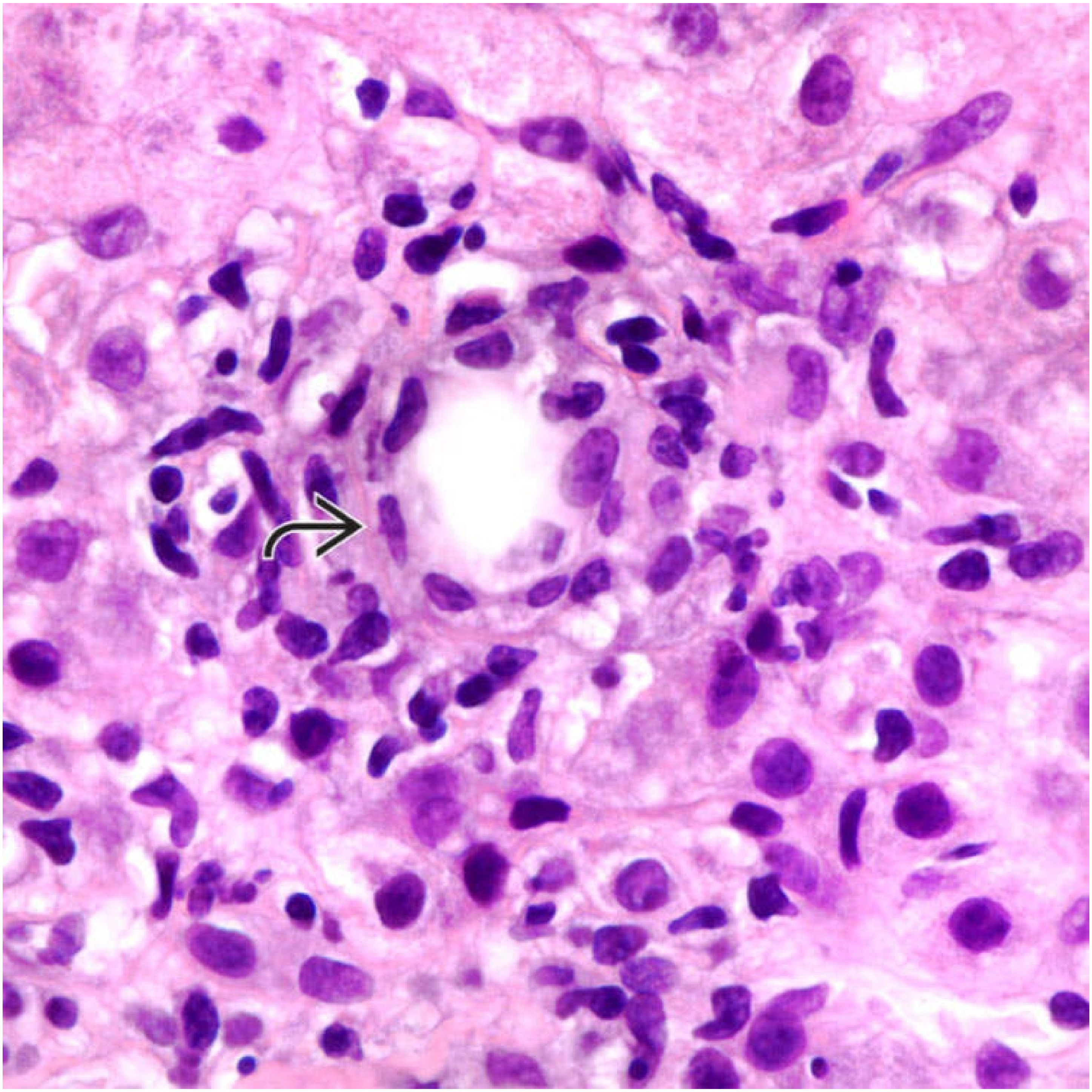
Poorly Formed Noncaseating Granuloma
A poorly formed granuloma in a MAC infection appears as a rounded cellular aggregate of histiocytes with ill-defined borders. Caseation is rare in MAC infections.



Necrotic Abscess
Liver biopsy in a patient with Mycobacterium kansasii infection shows a mixture of necrosis, histiocytes, and acute inflammation without well-formed granulomas.

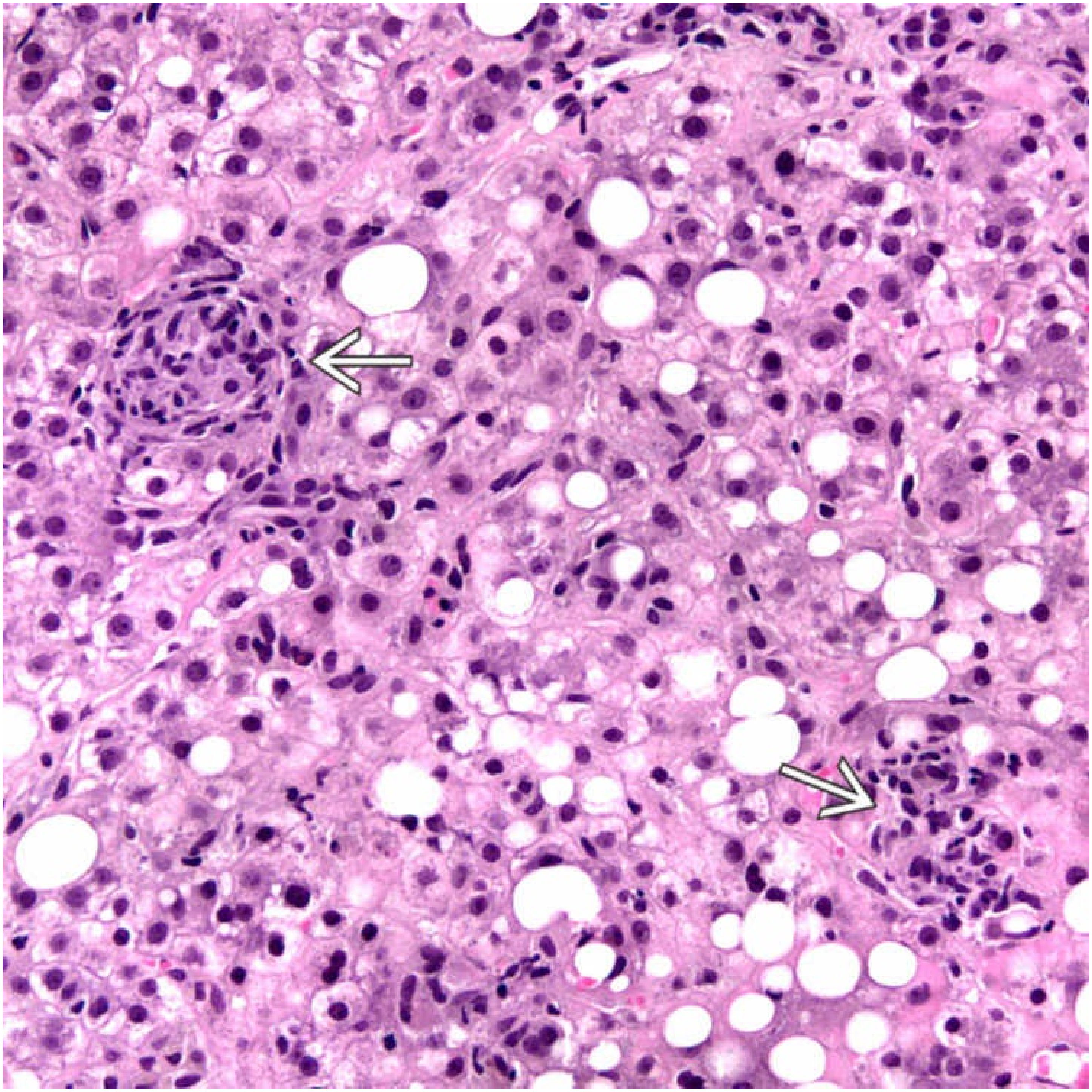


Numerous Organisms on AFB Stain
An acid-fast stain from a liver biopsy from a patient with M. kansasii infection shows a large number of acid-fast bacilli → that are long, slender, and beaded.



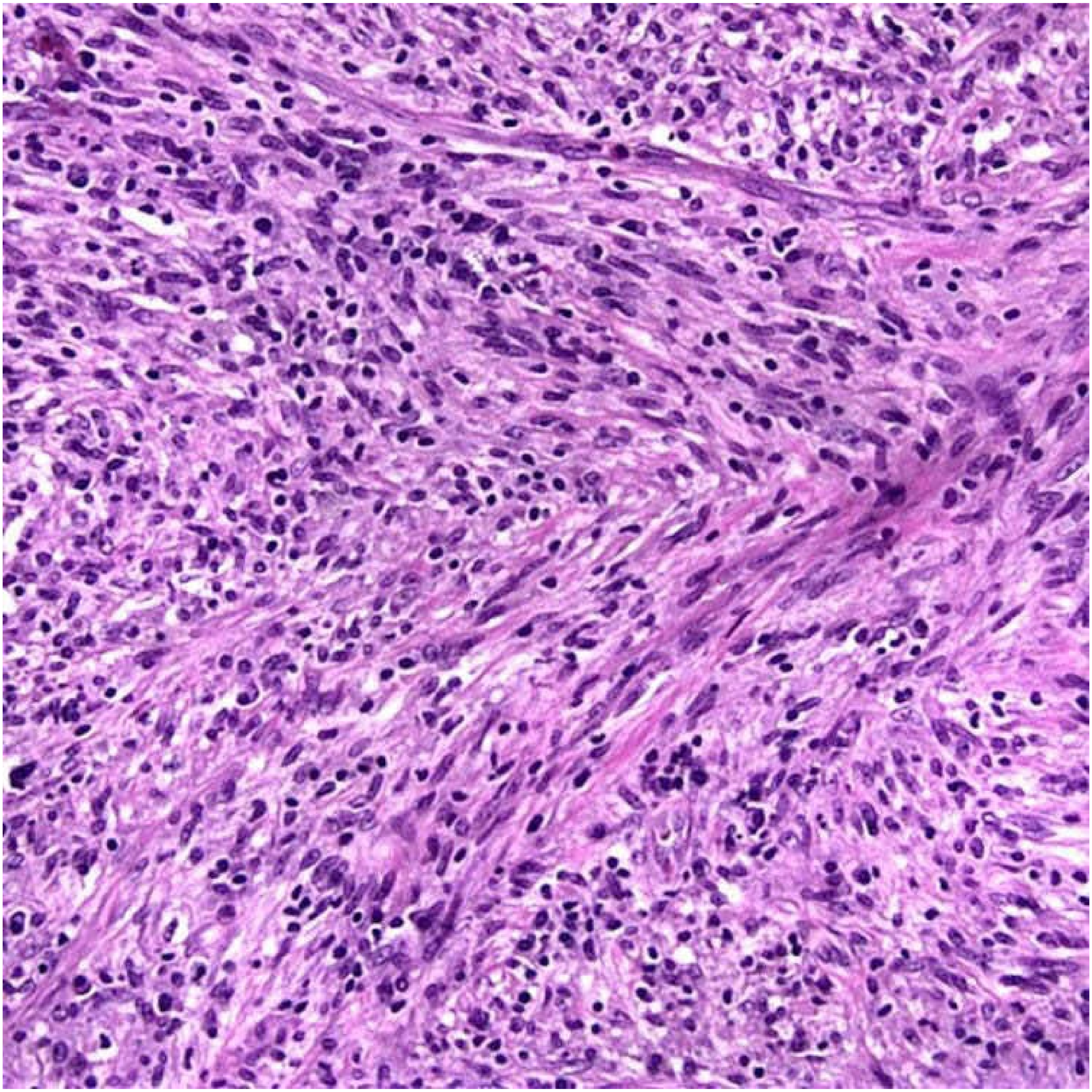
Fibrin Ring Granuloma

A fibrin ring granuloma is present in a patient with a MAC infection. Note the central lipid vacuole surrounded by a layer of histiocytes, a ring of fibrin, and more peripheral histiocytes.

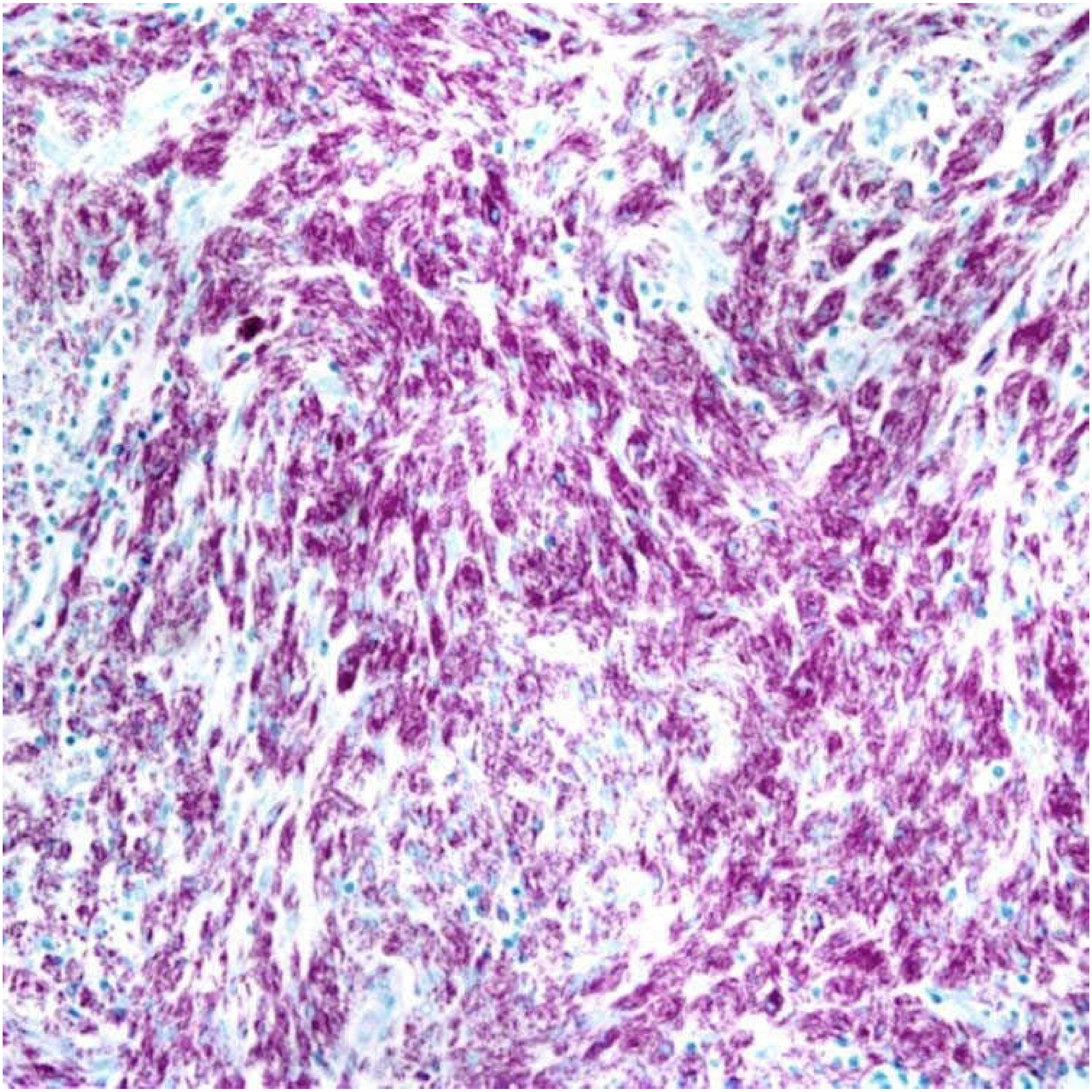


Microgranulomas

In this liver biopsy from an AIDS patient with a disseminated MAC infection, there are microgranulomas (small clusters of histiocytes) ⇒ in a background of steatosis.



Mycobacterial Spindle Cell Pseudotumor
Higher power view of a spindle cell pseudotumor shows a cellular lesion composed of spindled macrophages.



Spindle Cell Pseudotumor on AFB Stain
Innumerable acid fast organisms are seen within histiocytes in this mycobacterial spindle cell pseudotumor. These cells may stain with desmin, actin, or keratins in addition to macrophage markers and, thus, may be mistaken for a neoplasm.

SELECTED REFERENCES

1. Mogambery, JC, et al. Nontuberculous mycobacteria immune reconstitution syndrome. *Case Rep Med*. 2014; 2014:964612.
4. Horsburgh, CR, Jr. The pathophysiology of disseminated Mycobacterium avium complex disease in AIDS. *J Infect Dis*. 1999; 179(Suppl 3):S461–S465.
5. Flegg, PJ, et al. Disseminated disease due to Mycobacterium avium complex in AIDS. *QJM*. 1995; 88(9):617–626.

6. Torriani, FJ, et al. Autopsy findings in AIDS patients with Mycobacterium avium complex bacteremia. *J Infect Dis*. 1994; 170(6):1601–1605.
8. Inderlied, CB, et al. The Mycobacterium avium complex. *Clin Microbiol Rev*. 1993; 6(3):266–310.
9. Farhi, DC, et al. Pathologic findings in disseminated Mycobacterium avium-intracellulare infection. A report of 11 cases. *Am J Clin Pathol*. 1986; 85(1):67–72.

2. Rahmani, M, et al. Mycobacterial pseudotumor of the skin. *Virchows Arch*. 2013; 463(6):843–846.
3. Khatter, S, et al. Mycobacterial infections in human immuno-deficiency virus seropositive patients: role of non-tuberculous mycobacteria. *Indian J Tuberc*. 2008; 55(1):28–33.
7. Chin, DP. Mycobacterium avium complex and other nontuberculous mycobacterial infections in patients with HIV. *Semin Respir Infect*. 1993; 8(2):124–138.
10. Young, LS, et al. Mycobacterial infections in AIDS patients, with an emphasis on the Mycobacterium avium complex. *Rev Infect Dis*. 1986; 8(6):1024–1033.

Cat-Scratch Disease

KEY FACTS

Terminology

- Infection by *Bartonella* species after inoculation by cat
  - Zoonotic infection caused by small, weakly gram-negative coccobacillus
  - Most cases are attributed to *B. henselae*

Clinical Issues

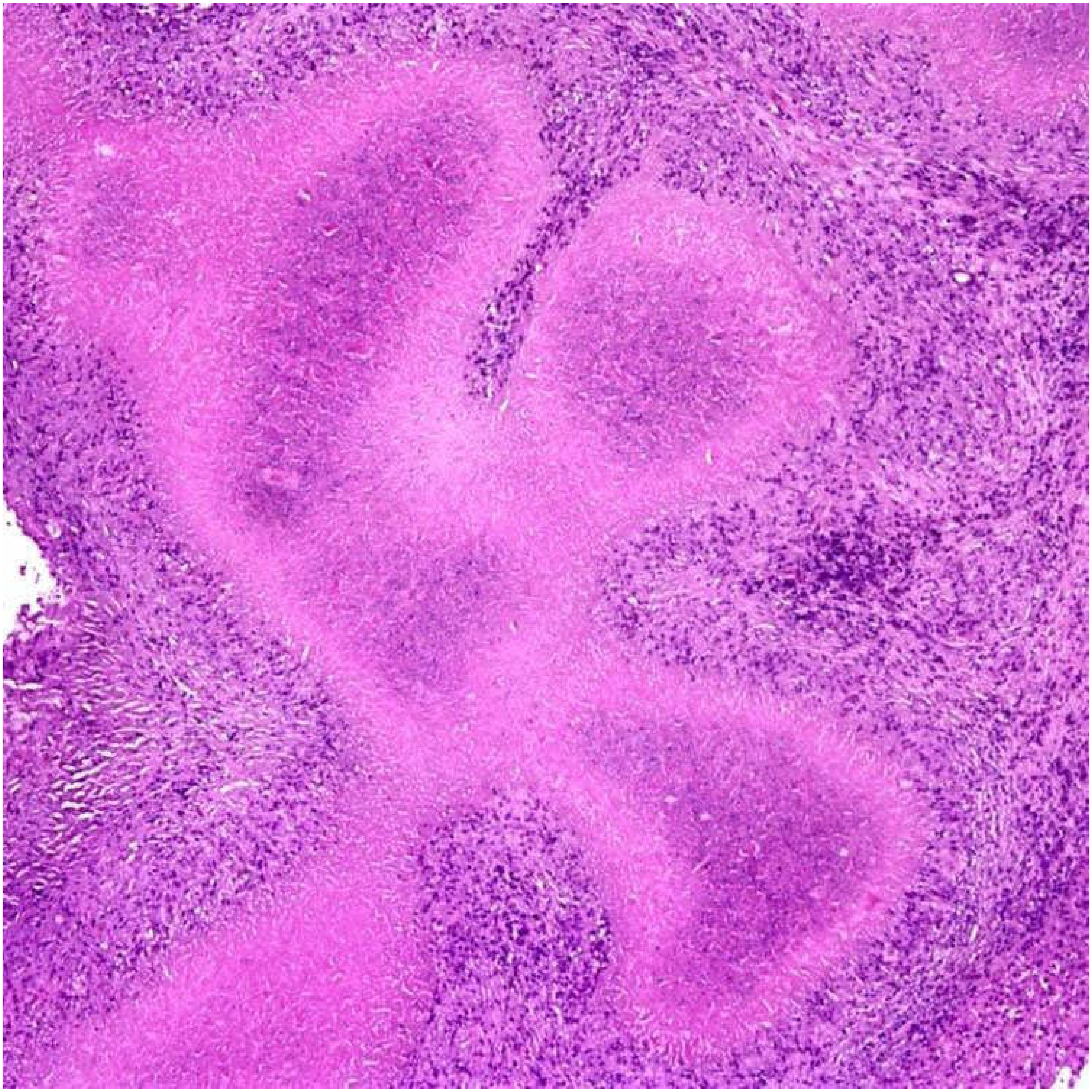
- Most cases are children and young adults with history of cat exposure
  - Usually not immunocompromised
- ~ 1-2% of patients develop visceral involvement (liver, spleen, bone, central nervous system, or lung)
  - Cutaneous inoculation site often absent in patients with visceral disease
- Multiple hepatic lesions, sometimes accompanied by splenic lesions and lymphadenopathy, raises concern for neoplasia
- Serologies useful in some cases
  - Limited sensitivity/specificity
  - Cross reactivity with other bacteria
- Excellent prognosis
  - Several antibiotics are effective

Microscopic

- Irregular, stellate microabscesses with central necrosis
  - Surrounding layers of palisading histiocytes, mononuclear cells, and rim of fibrous tissue
  - Fibrosis may be particularly prominent in liver

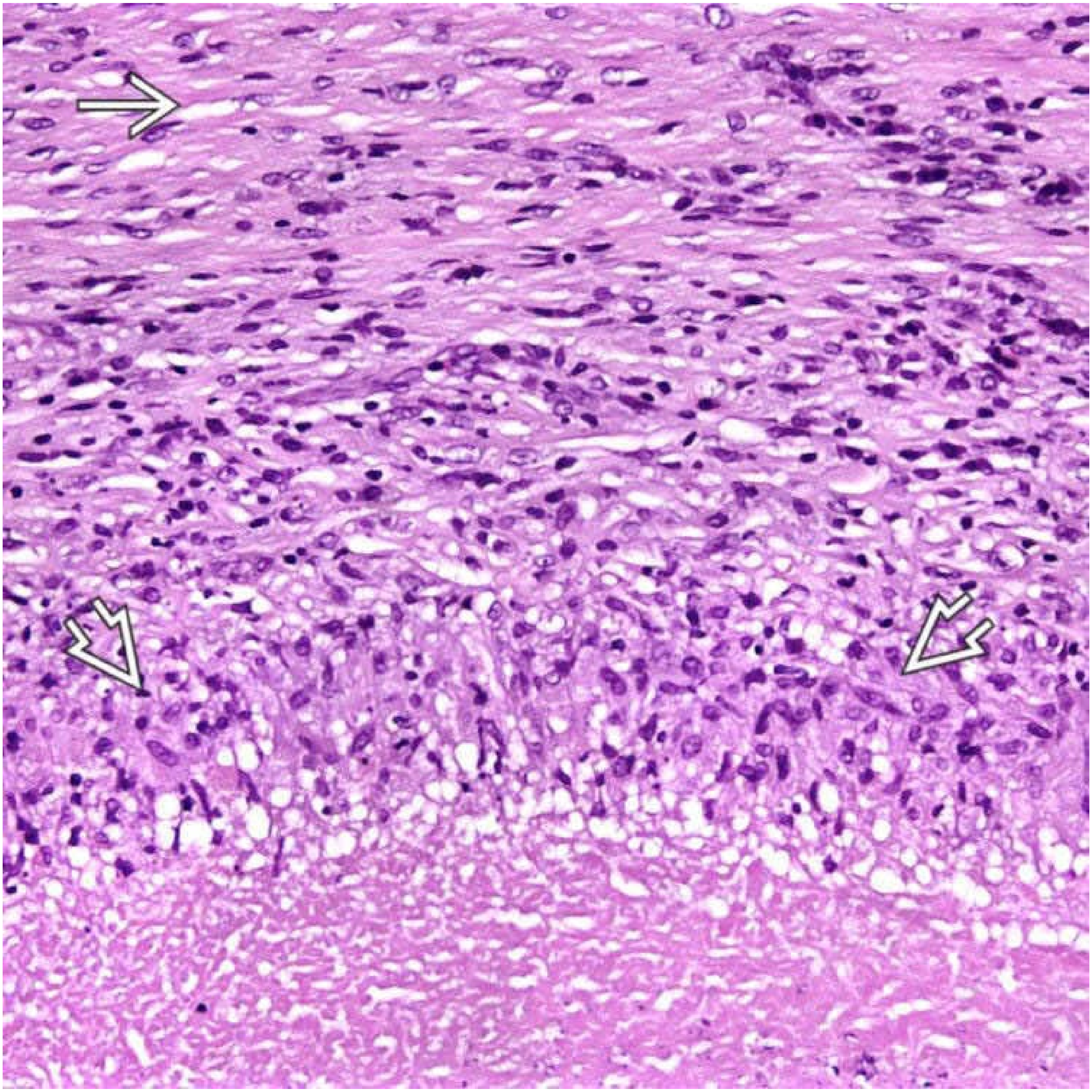
Ancillary Tests

- Silver impregnation stains
  - Warthin-Starry, Dieterle
- PCR
  - Can be performed from tissue block, blood, node aspirate, or fresh tissue

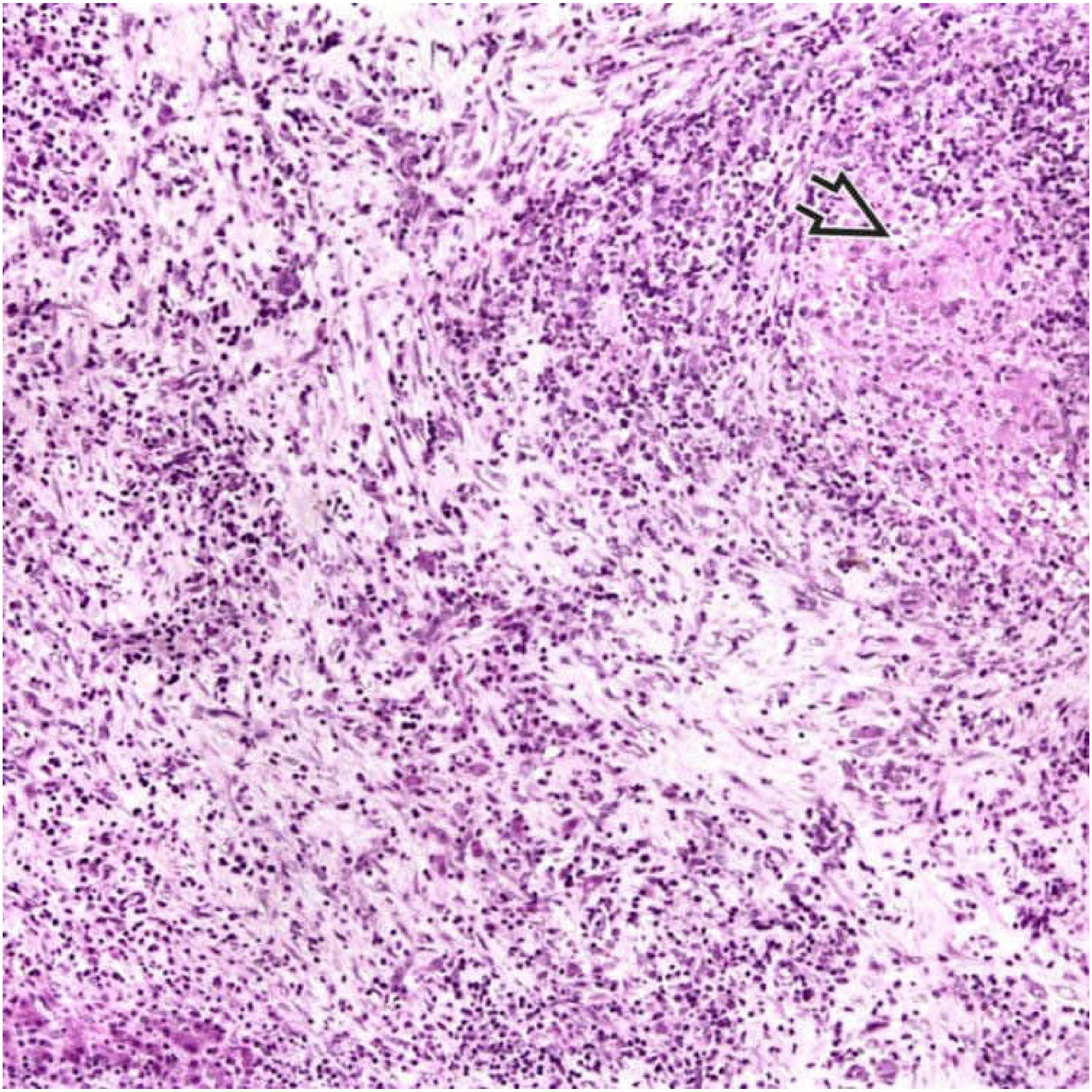


Stellate Microabscess

The characteristic lesion of hepatic cat-scratch disease consists of a stellate or geographic area of central necrosis surrounded by palisading histiocytes, mononuclear cells, and an outer rim of fibrosis. Younger lesions have less fibrosis and are more cellular.

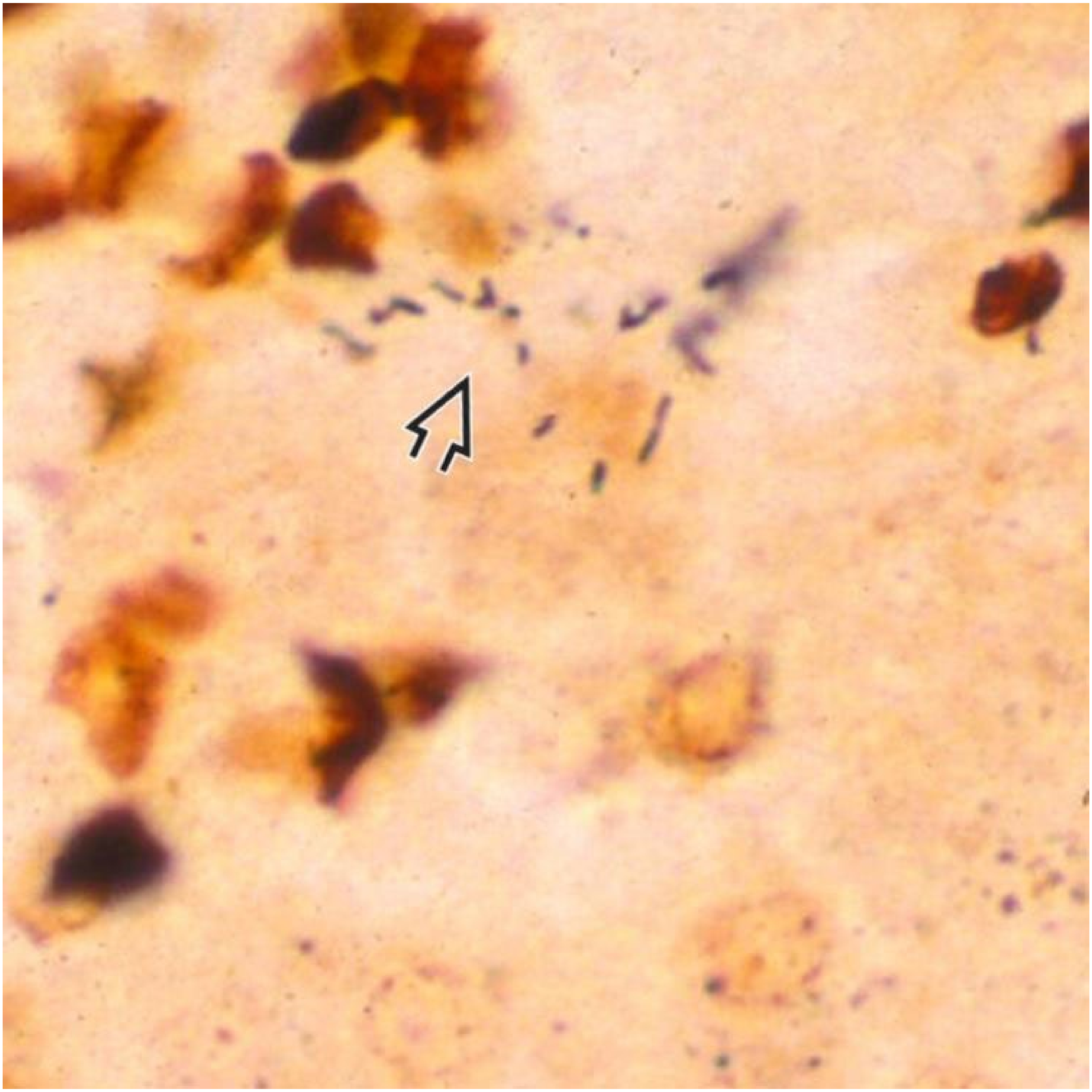


Layered Appearance of Lesion
The lesion of hepatic cat-scratch disease shows distinctive layers: Central necrosis, palisading histiocytes ⇨ and admixed mononuclear cells, and an outer rim of fibrosis ⇨ .



Older Lesion With More Fibrosis

Older lesions of hepatic cat-scratch disease may consist primarily of fibrosis and chronic inflammation with little remaining central necrosis ➪. A needle biopsy that samples only the fibrotic areas would most likely be nondiagnostic.



Warthin-Starry Stain
Occasionally, pleomorphic coccobacilli ➩ characteristic of Bartonella can be seen on a silver impregnation stain, such as a Warthin-Starry. (Courtesy M. Scott, MD.)

TERMINOLOGY

Abbreviations

- Cat-scratch disease (CSD)

Definitions

- Infection by *Bartonella* species after inoculation by cat

- Zoonotic infection caused by small, weakly gram-negative coccobacillus
- Most cases are attributed to *B. henselae* but *B. quintana* and other species have been implicated in some
  - *B. henselae* has been isolated from blood of both cats and their fleas

CLINICAL ISSUES

Epidemiology

- Age
  - Majority of patients are children and young adults
    - Typically not immunocompromised

Presentation

- Most patients present with cutaneous inoculation site and regional lymphadenopathy
  - ~ 1-2% of patients develop visceral involvement (liver, spleen, bone, central nervous system, or lung)
    - ~ 25% of patients with hepatic CSD have lymphadenopathy, but often skin papule is absent in visceral disease
- Nonspecific symptoms, including fever, abdominal pain, chills, headache, malaise, and weight loss
- Presence of hepatic nodules, with splenic nodules and lymphadenopathy in some cases, raises concern for neoplasia

Laboratory Tests

- Serologies
  - Sensitivity: 80-100%; specificity: 89-99%
  - Cross reactivity with other bacteria is a problem
  - May get false-negatives in very young children, elderly patients, immunocompromised patients
- Skin test
  - No longer used
- PCR of tissue, blood, or lymph node aspirate
- Very difficult to culture

Treatment

- Drugs
  - Several antibiotics are effective (rifampin, erythromycin, ciprofloxacin, doxycycline)

Prognosis

- Excellent; typically no long-term hepatic dysfunction

MACROSCOPIC

General Features

- Liver may be studded with hard nodules of varying sizes

MICROSCOPIC

Histologic Features

- Irregular, stellate microabscesses
  - Surrounded by layers of palisading histiocytes, lymphocytes, and outer rim of fibrous tissue
- Temporal heterogeneity
  - Younger lesions may show more necrosis with less organization of inflammatory granulomatous response
  - Older lesions may show confluent granulomas with scarring and scant residual necrosis
- Occasional small rounded granulomas with giant cells and small foci of central necrosis that can mimic caseating granulomas in mycobacterial or fungal infections

Predominant Pattern/Injury Type

- Inflammatory, granulomatous

ANCILLARY TESTS

Histochemistry

- Silver impregnation stains (Warthin-Starry, Dieterle)
  - Positive in some cases; organisms often cluster around vessels or in areas of necrosis
  - Difficult to distinguish between organisms and nonspecific silver precipitate

Immunohistochemistry

- Recently developed IHC antibody
  - Not widely used; less sensitive than PCR

PCR

- PCR from formalin-fixed, paraffin-embedded tissue or fresh tissue

DIFFERENTIAL DIAGNOSIS

Granulomatous Infections of Liver

- *Yersinia enterocolitica*, *Francisella tularensis*, *Mycobacterium*, *Candida*, and *Actinomyces* infection may produce similar lesions

- Culture &/or identification of organism in tissue using histochemical stains or molecular studies may be necessary to distinguish between these infections

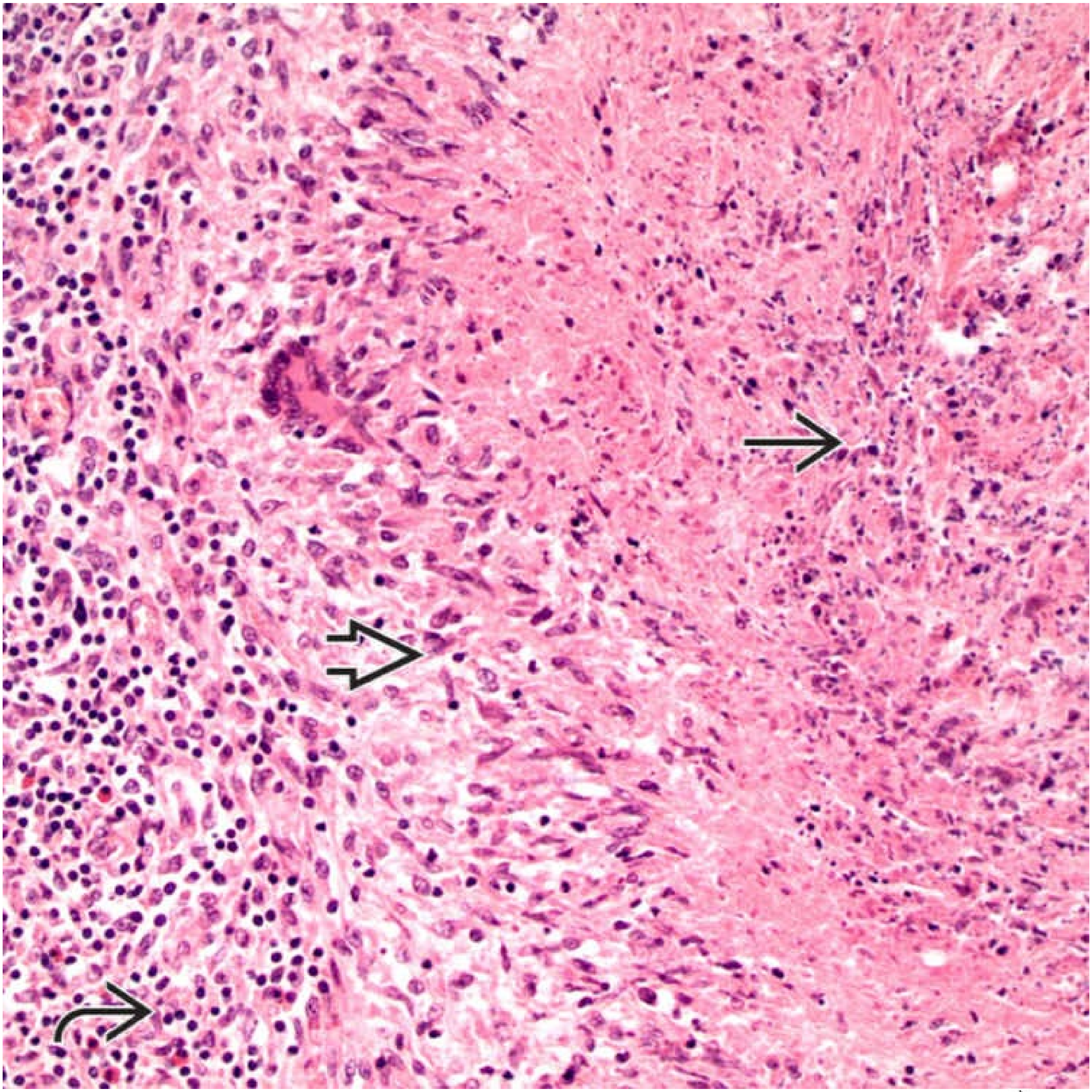
Sarcoidosis

- Nonnecrotizing granulomas, typically does not occur in children

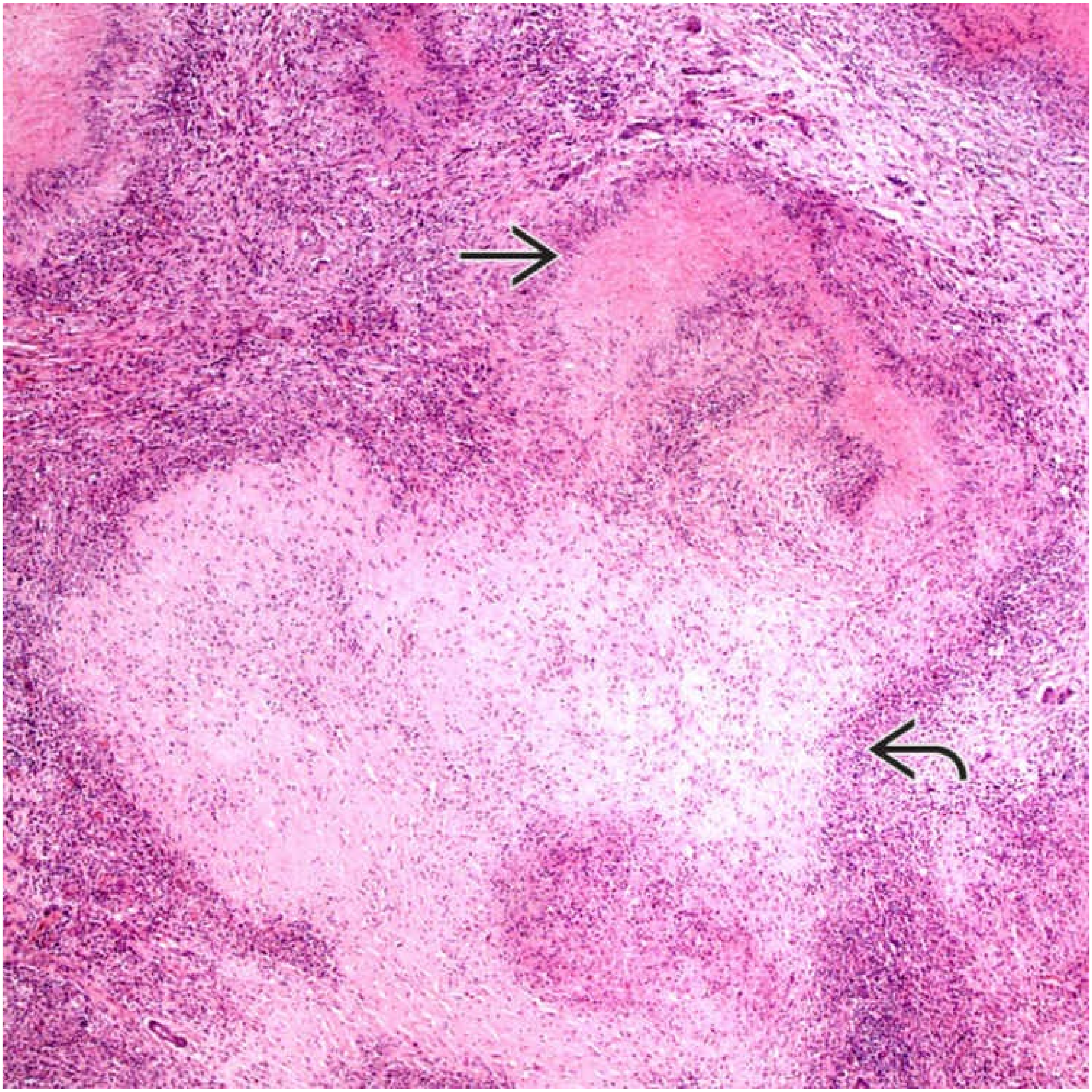
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

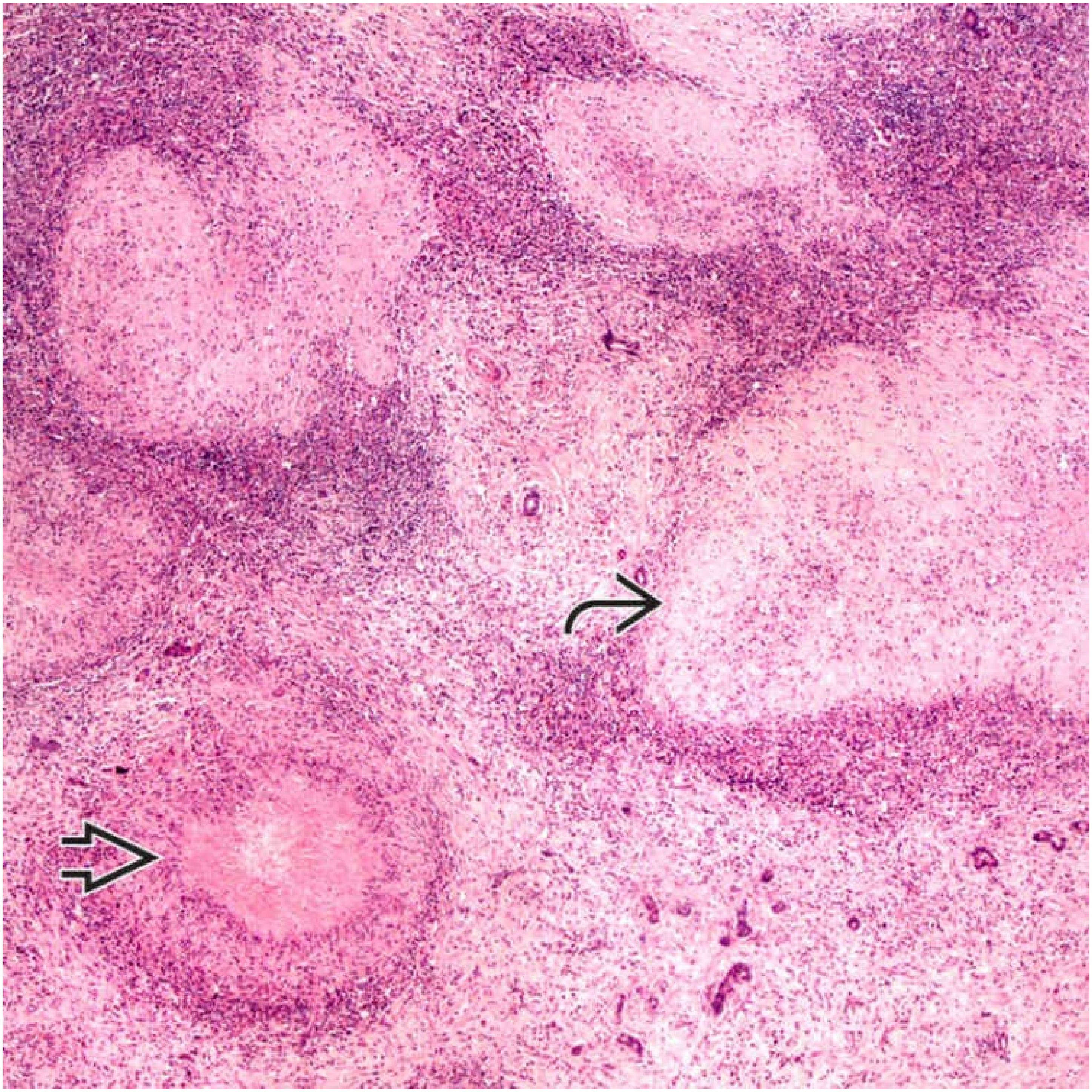
- Layered stellate microabscess with prominent fibrotic rim is highly characteristic
- Needle biopsy may only sample fibrosis, and, thus, wedge biopsy may be required for diagnosis



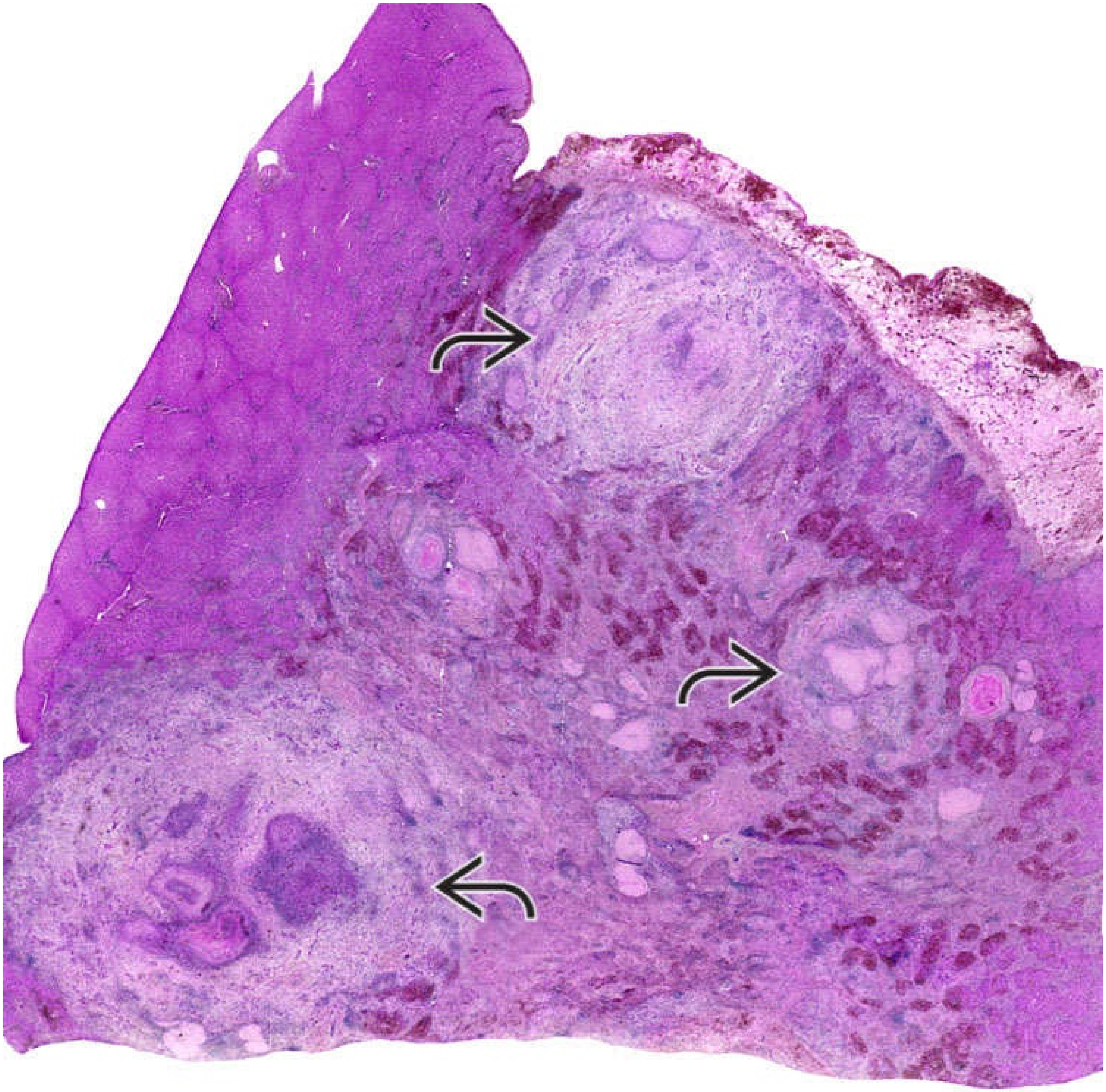
H&E-stained section at high magnification shows a stellate microabscess with central necrotic region → surrounded by a rim of palisaded histiocytes ⇨ and lymphocytes ↷ .



This low-power view of a liver biopsy shows a stellate abscess with central necrosis, lined by palisading histiocytes and lymphocytes → in continuity with fibrotic areas ↷ .



The lesions of hepatic cat scratch disease are often at various stages of evolution, including young lesions with central necrosis and older, more fibrotic lesions .



This liver wedge excision shows several nodules of granulomatous inflammation ↷ with stellate abscesses and fibrosis.

SELECTED REFERENCES

1. Klotz, SA, et al. Cat-scratch disease. *Am Fam Physician*. 2011; 83(2):152–155.
2. Laham, FR, et al. Hepatosplenic cat-scratch fever. *Lancet Infect Dis*. 2008; 8(2):140.
3. Scolfaro, C, et al. Prolonged follow up of seven patients affected by hepatosplenic granulomata due to cat-scratch disease. *Eur J Pediatr*. 2008; 167(4):471–473.
4. Ventura, A, et al. Systemic Bartonella henselae infection with hepatosplenic involvement. *J Pediatr Gastroenterol Nutr*. 1999; 29(1):52–56.
5. Lamps, LW, et al. The histologic spectrum of hepatic cat scratch disease. A series of six cases with confirmed Bartonella henselae infection. *Am J Surg Pathol*. 1996; 20(10):1253–1259.

7. Malatack, JJ, et al. Cat-scratch disease without adenopathy. *J Pediatr*. 1989; 114(1):101–104.
8. Lenoir, AA, et al. Granulomatous hepatitis associated with cat scratch disease. *Lancet*. 1988; 1(8595):1132–1136.

6. Liston, TE, et al. Granulomatous hepatitis and necrotizing splenitis due to Bartonella henselae in a patient with cancer: case report and review of hepatosplenic manifestations of bartonella infection. *Clin Infect Dis*. 1996; 22(6):951–957.

Candidiasis

KEY FACTS

Terminology

- Candidiasis is most common disseminated fungal infection in immunocompromised hosts
  - Liver involvement is common
  - Rare in immunocompetent patients

Etiology/Pathogenesis

- *Candida albicans* most common
  - Endogenous commensal that is part of normal flora of GI tract, mouth, respiratory tract, vagina
- Risk factors include disruption of mucosal or cutaneous barriers, immunosuppression, use of broad-spectrum antibiotics

Clinical Issues

- Presentation may be very nonspecific (fever, hepatomegaly, abdominal pain)
- Prognosis depends on underlying immune status of patient

Macroscopic

- Yellow-white nodules
  - Usually multiple, 1-2 cm

Microscopic

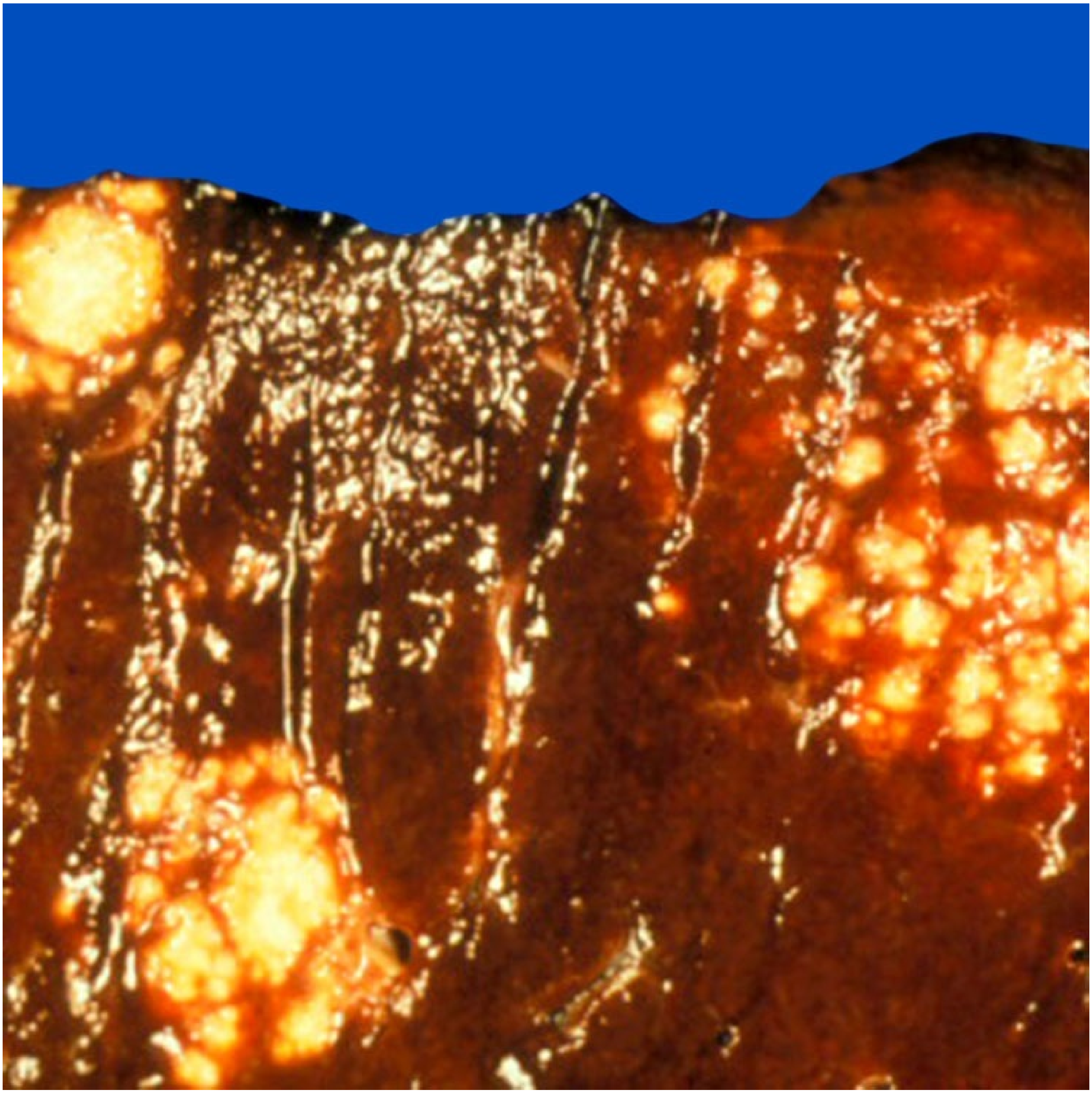
- Typical inflammatory reaction is granulomatous
  - Frequently with suppurative/necrotic center
  - May have minimal inflammation in severely immunocompromised patients
- Mixture of budding yeast, hyphae, and pseudohyphae
  - GMS, PAS positive

Ancillary Tests

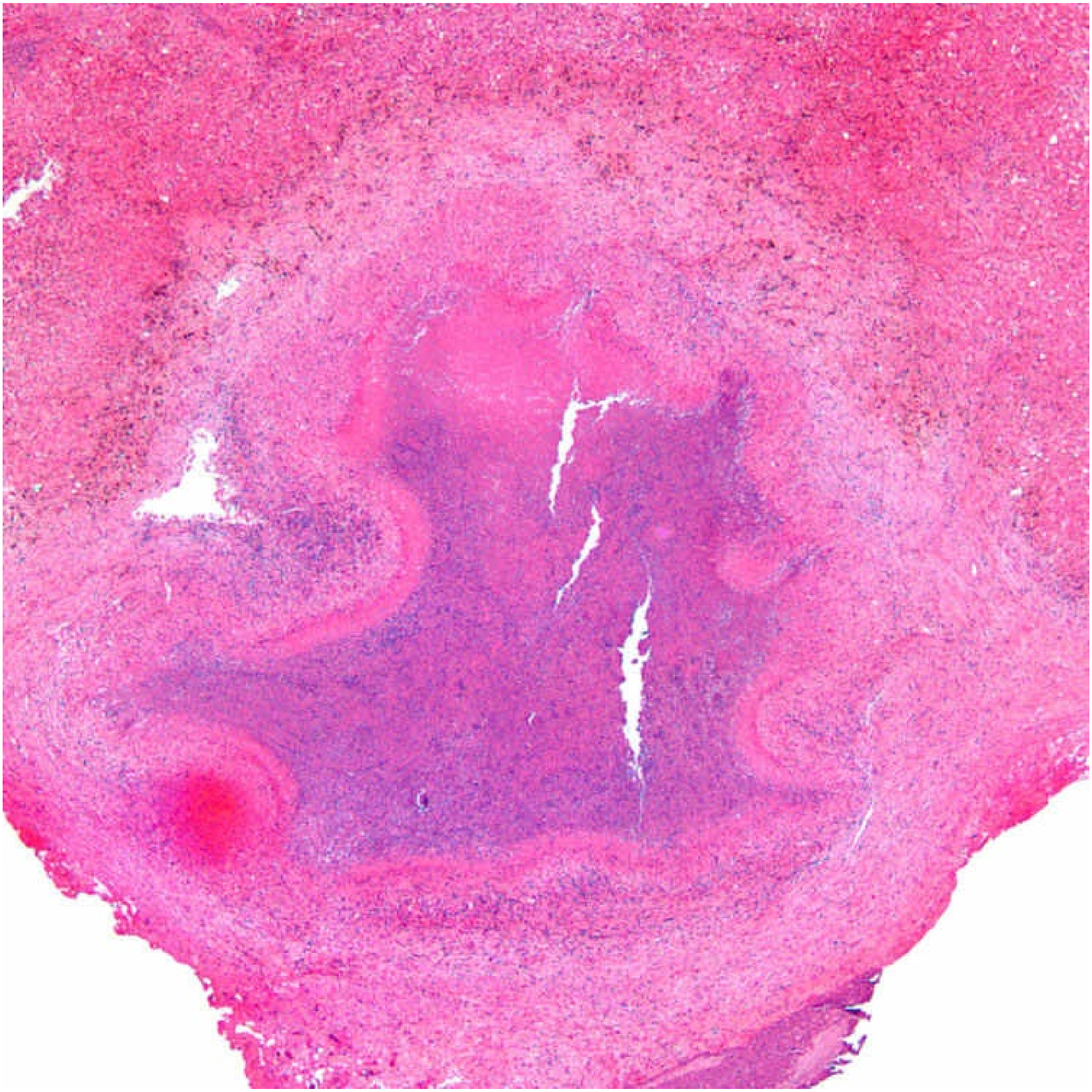
• PCR
• Culture

Diagnostic Checklist

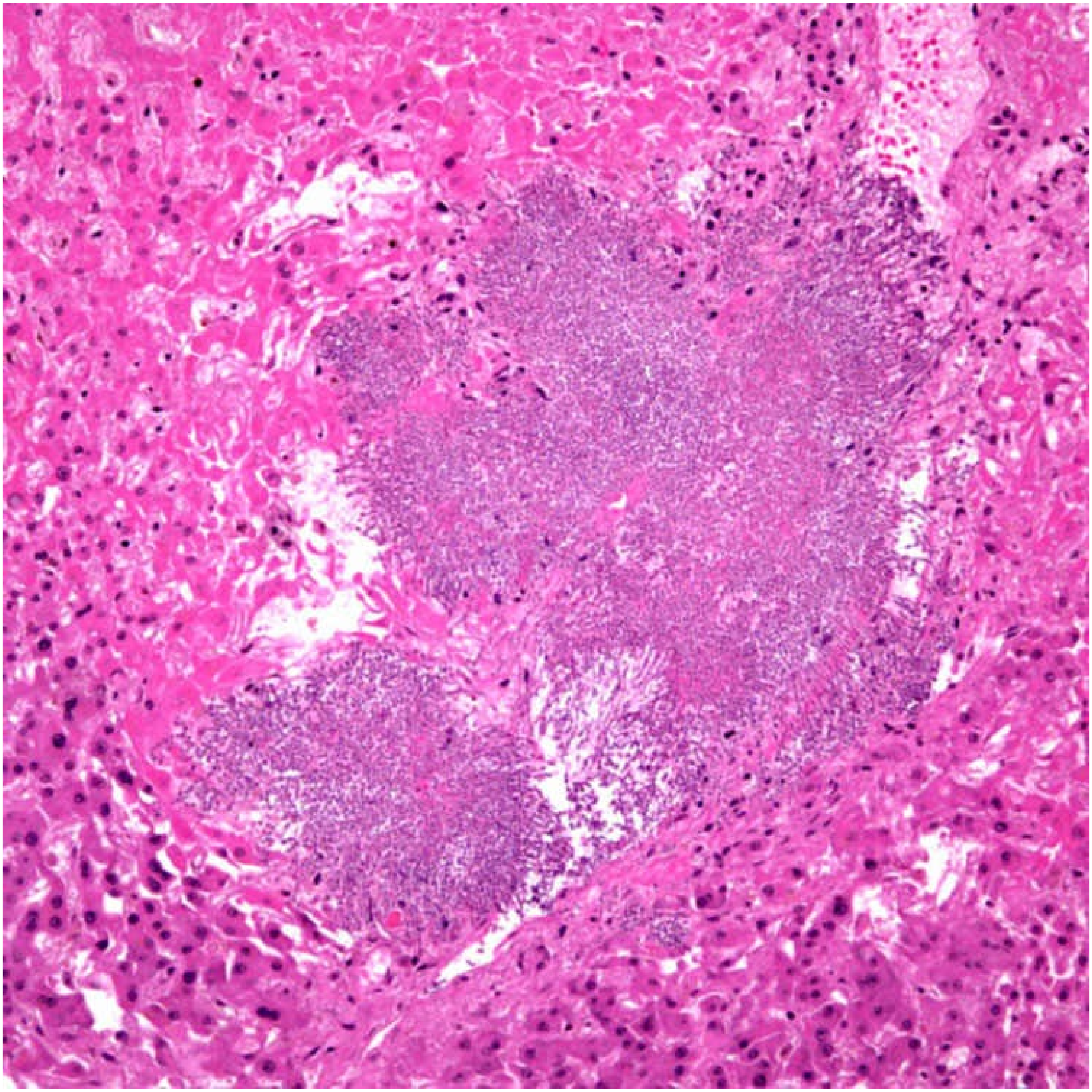
• Fungi can sometimes be speciated by morphology but need confirmatory test



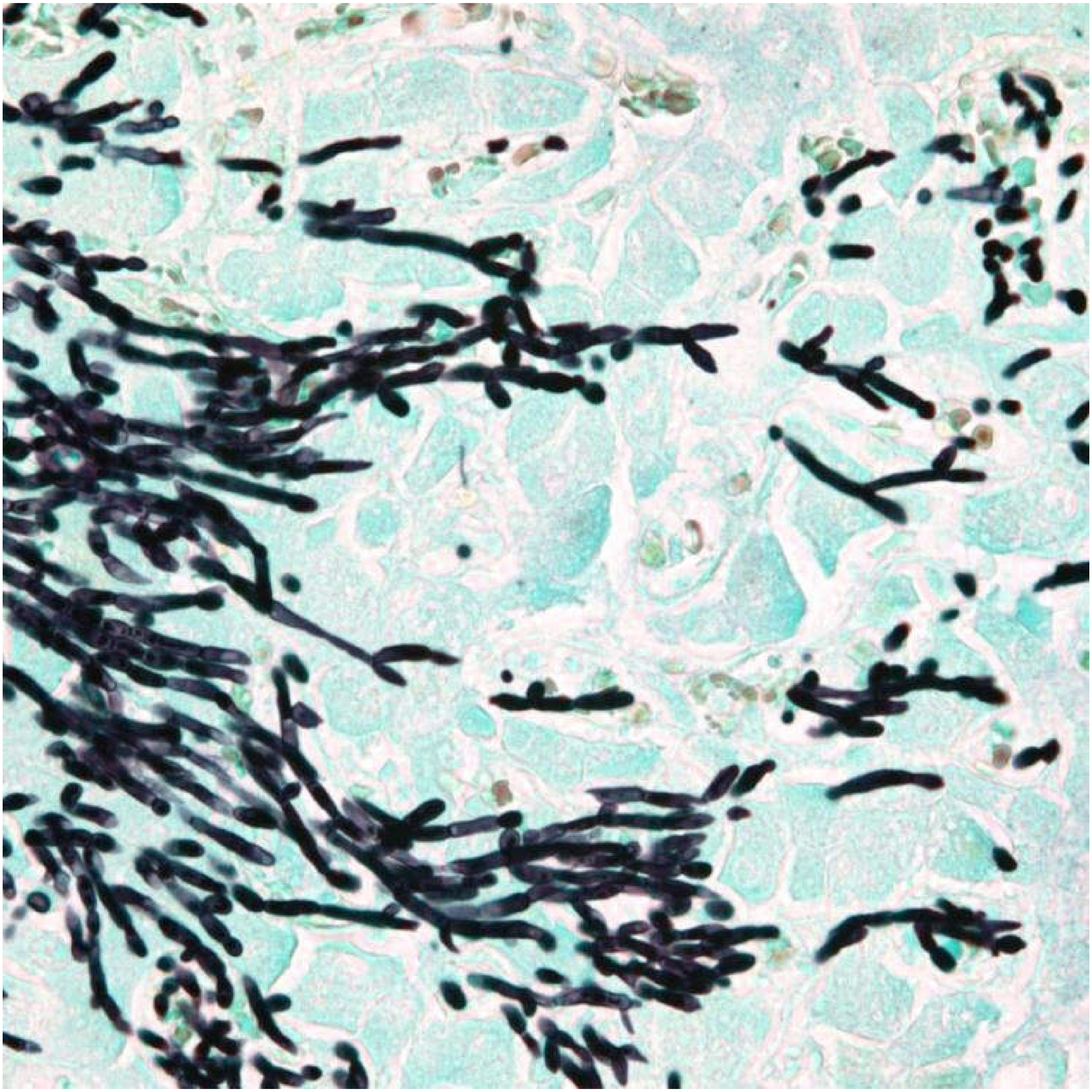
Gross Appearance
Gross photograph shows a liver from an autopsy showing multiple yellow-white Candida lesions. Multiple 1- to 2-cm yellow-white nodules is a typical gross appearance of hepatic candidiasis.



Hepatic *Candida* Abscess
H&E section shows a stellate Candida abscess with central necrosis and peripheral fibrosis in a liver wedge biopsy.



Necrosis but Minimal Associated Inflammation
This liver specimen shows a large cluster of Candida with associated necrosis, but minimal associated inflammation, in a severely immunocompromised patient. (Courtesy D. Milner, MD.)



Candida Morphology
This GMS stain shows the mixture of budding yeast, pseudohyphae, and occasional true hyphae that is typical of Candida albicans.

TERMINOLOGY

Definitions

- Infection of liver by *Candida* fungus
  - Most common disseminated fungal infection in immunocompromised hosts
  - Liver involvement is common in disseminated infection
  - – Rare in immunocompetent patients

ETIOLOGY/PATHOGENESIS

Infectious Agents

- *Candida* species
  - *Candida albicans* most common
  - – Endogenous commensal that is part of normal flora of GI tract, mouth, respiratory tract, vagina
- Other pathogenic *Candida* include*C. tropicalis*, *C. parapsilosis*, *C. krusei*
  - – Saprophytic yeasts present in both humans and environment
- *Candida* (*Torulopsis*) *glabrata*
  - – Normal flora of skin, GI tract, GU tract, respiratory tract
- Patients with hepatic infection almost always immunocompromised
  - In liver transplant patients, may be associated with ischemic/necrotic bile ducts, hepatic artery thrombosis

Risk Factors

- Disruption of mucosal or cutaneous barriers
- Broad-spectrum antibiotics
- Metabolic abnormalities
- Indwelling catheters/vascular devices
- Neutropenia, immunosuppression, steroids
- Neonates

CLINICAL ISSUES

Presentation

- Hepatomegaly, abdominal pain, fever
- Nonspecific presentation may delay diagnosis

Laboratory Tests

- Elevated transaminases and bilirubin

Treatment

- Drugs
  - Antifungals

Prognosis

- Depends on underlying immune status of patient

- Difficult to eliminate fungus
- Persistent lesions may produce scarring

MACROSCOPIC

General Features

- Multiple yellow-white, 1- to 2-cm nodules

MICROSCOPIC

Histologic Features

- Typical inflammatory reaction is granulomatous
  - Giant cells, palisading histiocytes, peripheral scarring are variably present
- Usually suppurative center ± necrosis
- Nonspecific reactive findings, usually near fungal lesion
  - Cholestasis
  - Mixed portal inflammation and ductular reaction
  - Sinusoidal dilatation
- Morphologic features of fungus
  - Mixture of budding yeast, hyphae, and pseudohyphae
    - *C. albicans*, *C. tropicalis*
  - Budding yeast only
    - *C.* (*Torulopsis*) *glabrata*
  - All are GMS, PAS positive

ANCILLARY TESTS

Laboratory Tests

- PCR
  - Can often be performed from formalin fixed, paraffin embedded block
- Culture
- ß-D-glucan in serum
  - Marker of disseminated infection/fungemia; not specific for *Candida*

DIFFERENTIAL DIAGNOSIS

Cat-Scratch Disease

- Similar palisading histiocytes, peripheral fibrosis, and central stellate suppuration
- GMS stain, laboratory tests negative for fungi
- PCR, silver impregnation stains to confirm *Bartonella*

Other Fungi

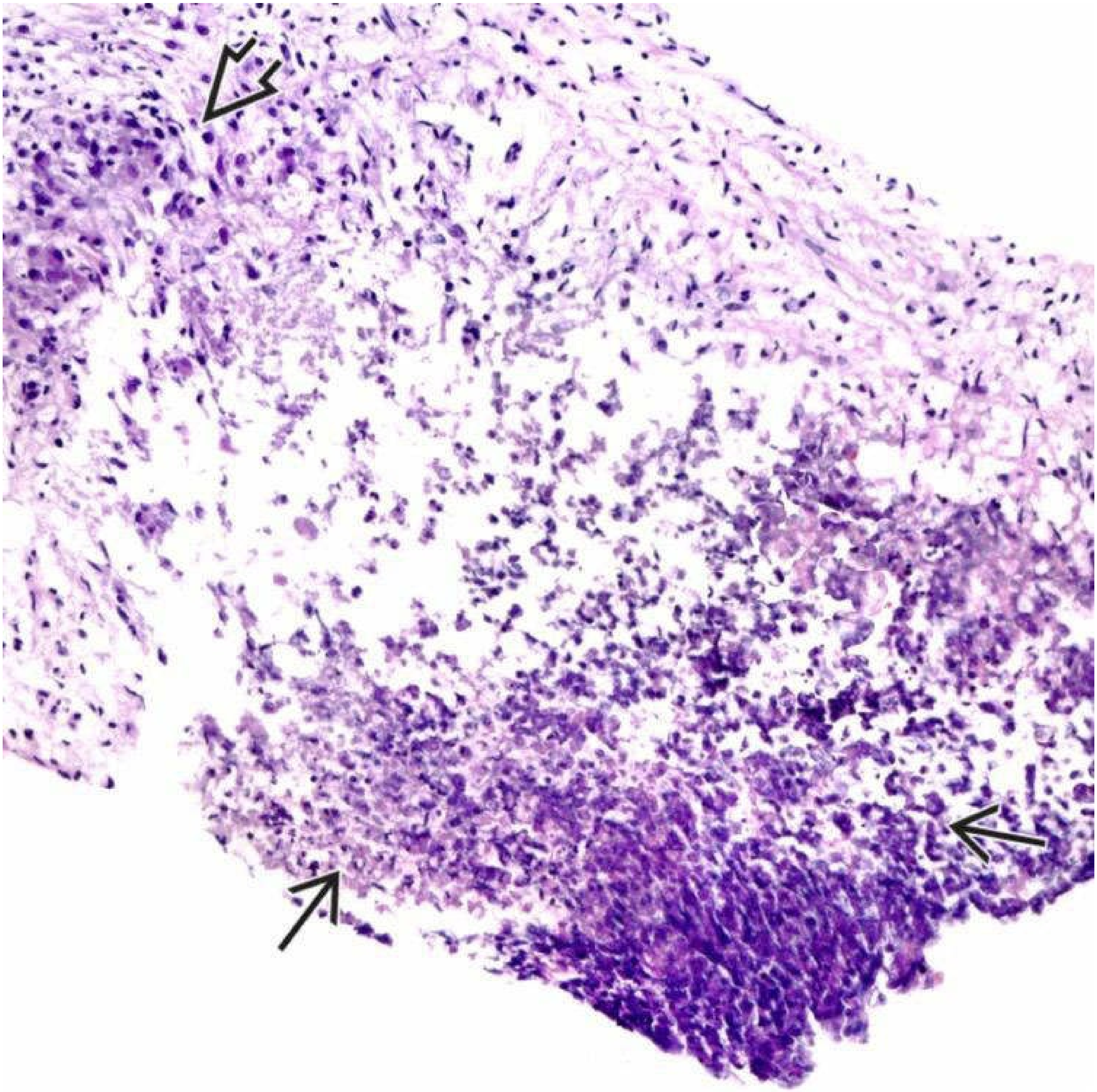
- *Aspergillus*
  - True hyphae that branch at acute angles, usually vasocentric
- Mucor
  - Broad, pauciseptate, ribbon-like hyphae; usually vasocentric
- Histoplasmosis
  - More uniform size than *C. (Torulopsis) glabrata*
  - “Halo” effect around organism in tissue

Necrotic Tumor

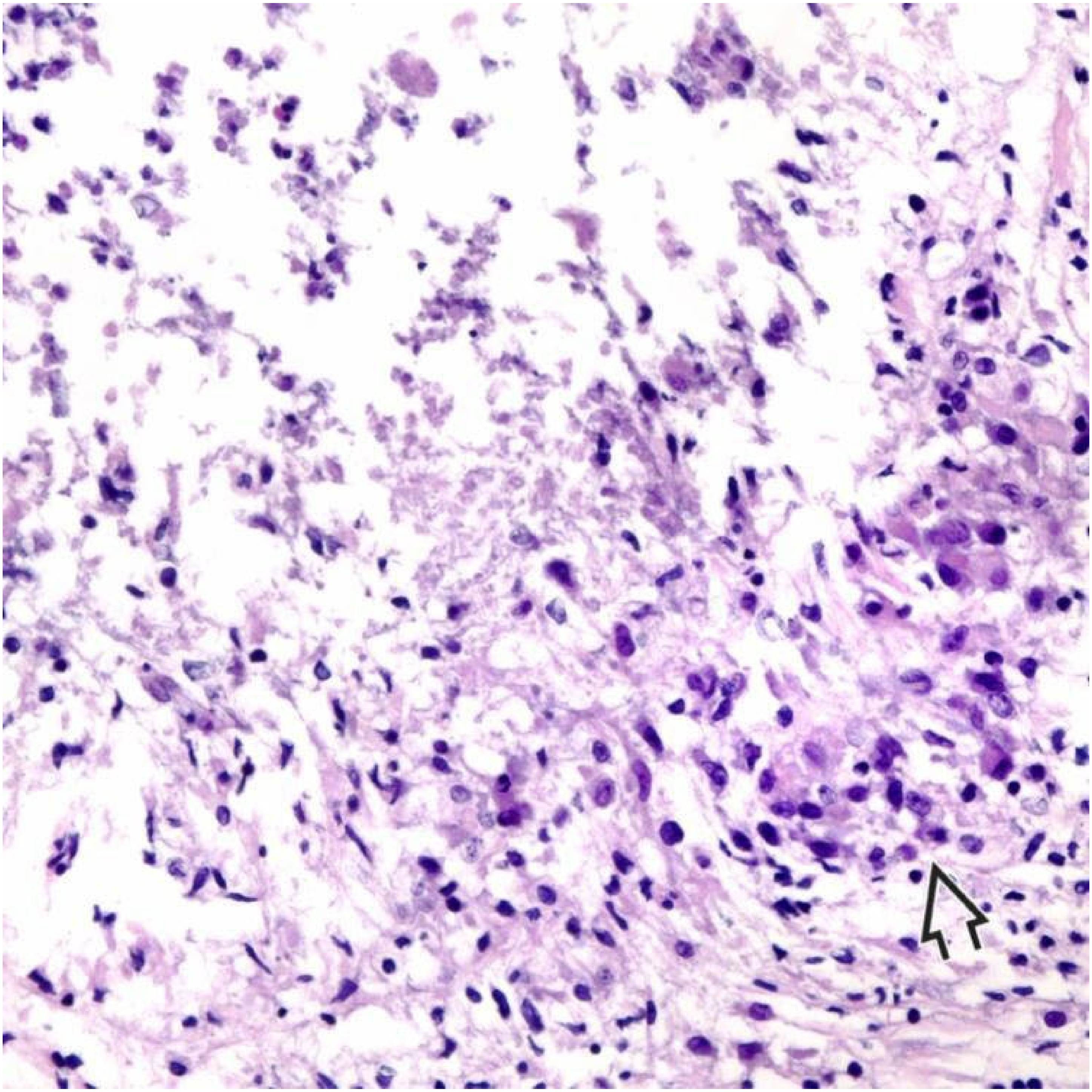
- GMS stain negative in malignancy

Bacterial Abscess

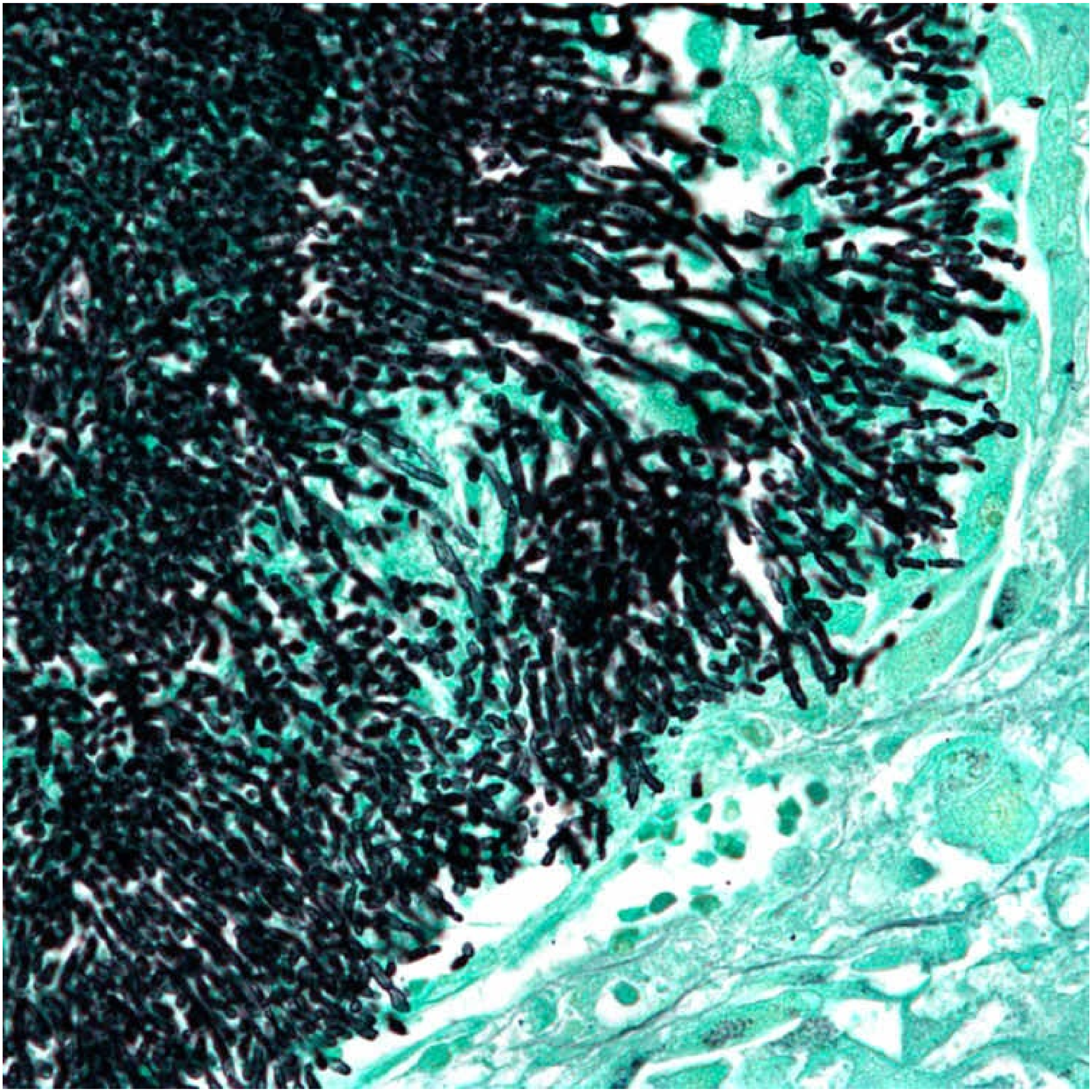
- GMS is negative for fungi
- Usually lacks granulomatous features

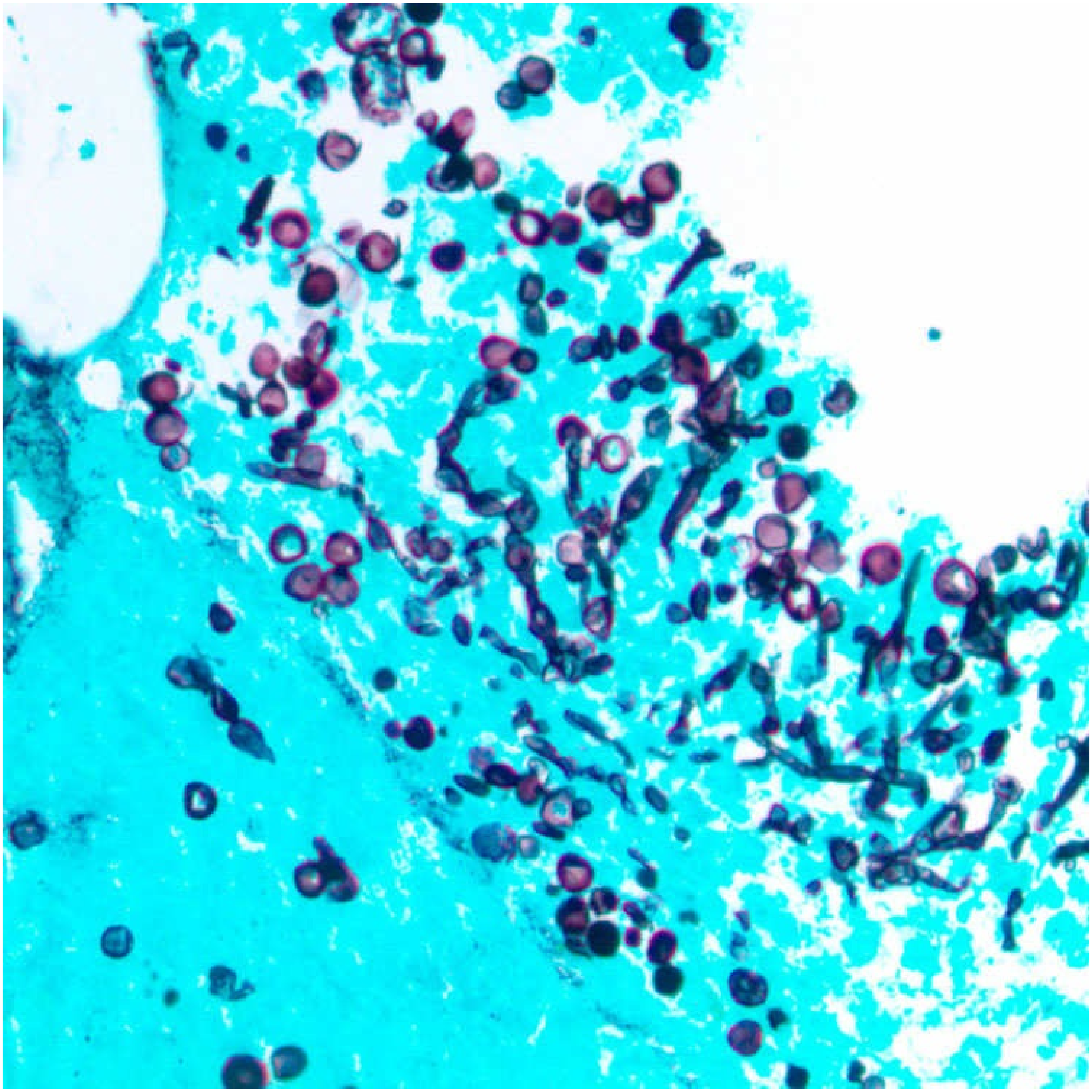


This liver biopsy shows an abscess → due to Candida, with a loosely formed granuloma at the periphery ⇨ .



A higher power view of a liver biopsy containing an abscess secondary to Candida shows a loose granuloma at the periphery of the abscess.


GMS stain highlights the Candida within a hepatic abscess. (Courtesy D. Milner, MD.)


GMS stain shows budding yeast and pseudohyphae in a Candida liver abscess.

SELECTED REFERENCES

1. Trubiano, JA, et al. Clinical utility of panfungal polymerase chain reaction for the diagnosis of invasive fungal disease: a single center experience. *Med Mycol*. 2016; 54(2):138–146.
2. Fung, JJ. Fungal infection in liver transplantation. *Transpl Infect Dis*. 2002; 4(Suppl 3):18–23.
3. Johnson, TL, et al. Candida hepatitis. Histopathologic diagnosis. *Am J Surg Pathol*. 1988; 12(9):716–720.
4. Thaler, M, et al. Hepatic candidiasis in cancer patients: the evolving picture of the syndrome. *Ann Intern Med*. 1988; 108(1):88–100.
5. Maksymiuk, AW, et al. Systemic candidiasis in cancer patients. *Am J Med*. 1984; 77(4D):20–27.

6. Hughes, WT. Systemic candidiasis: a study of 109 fatal cases. *Pediatr Infect Dis*. 1982; 1(1):11–18.

Histoplasmosis

KEY FACTS

Etiology/Pathogenesis

- *Histoplasma capsulatum* : Dimorphic fungus found in soil contaminated with bird or bat droppings
- Found in soil, particularly when contaminated with bird or bat droppings

Clinical Issues

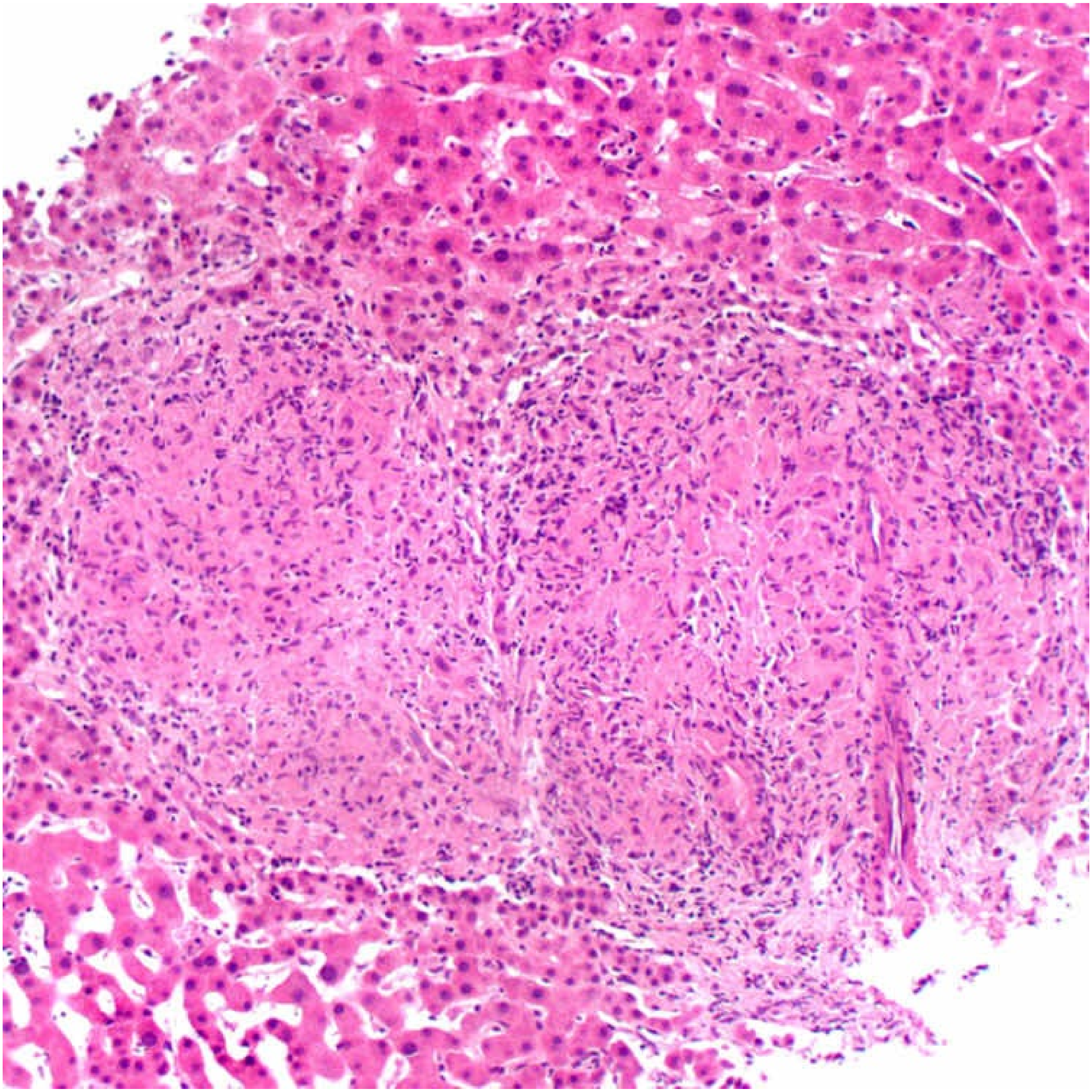
- Endemic in many parts of world, including Ohio and Mississippi River valleys
  - Most common endemic mycosis in United States
- Liver involvement is almost always part of disseminated infection
  - Patients often immunocompromised
  - Liver is involved in up to 90% of cases of disseminated disease
- With treatment, mortality rate is < 10%
- Most infections in immunocompetent persons are self-limited and often clinically unrecognized

Microscopic

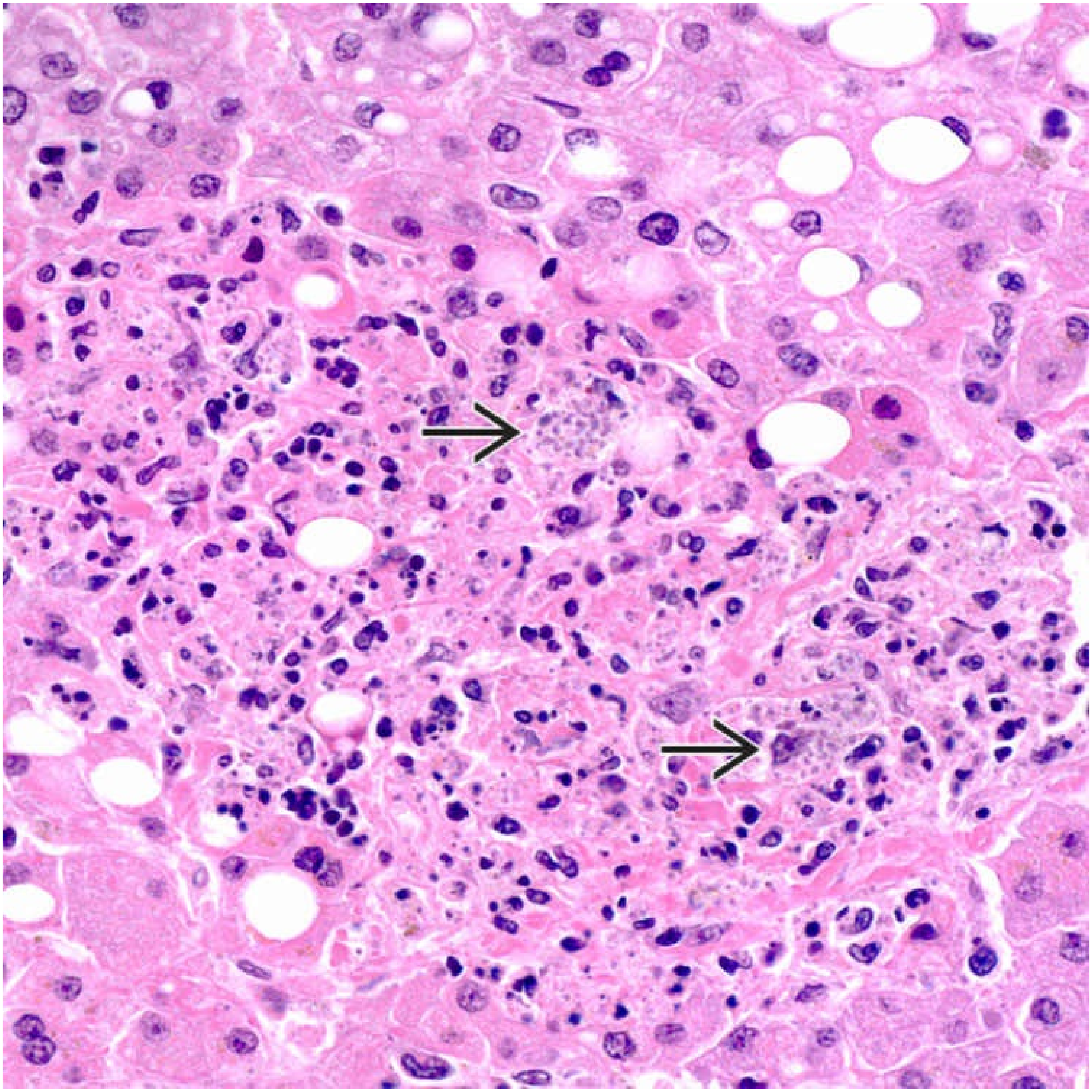
- Portal and lobular lymphohistiocytic inflammation is typical
  - Discrete granulomas variable present and often absent in immunocompromised patients
  - May have little or no inflammatory response in severely immunocompromised patients
- Large numbers of yeast are present in portal and sinusoidal macrophages
- Yeast are 2-4 µm, oval, with narrow-based budding
  - GMS and PAS/diastase positive

Top Differential Diagnoses

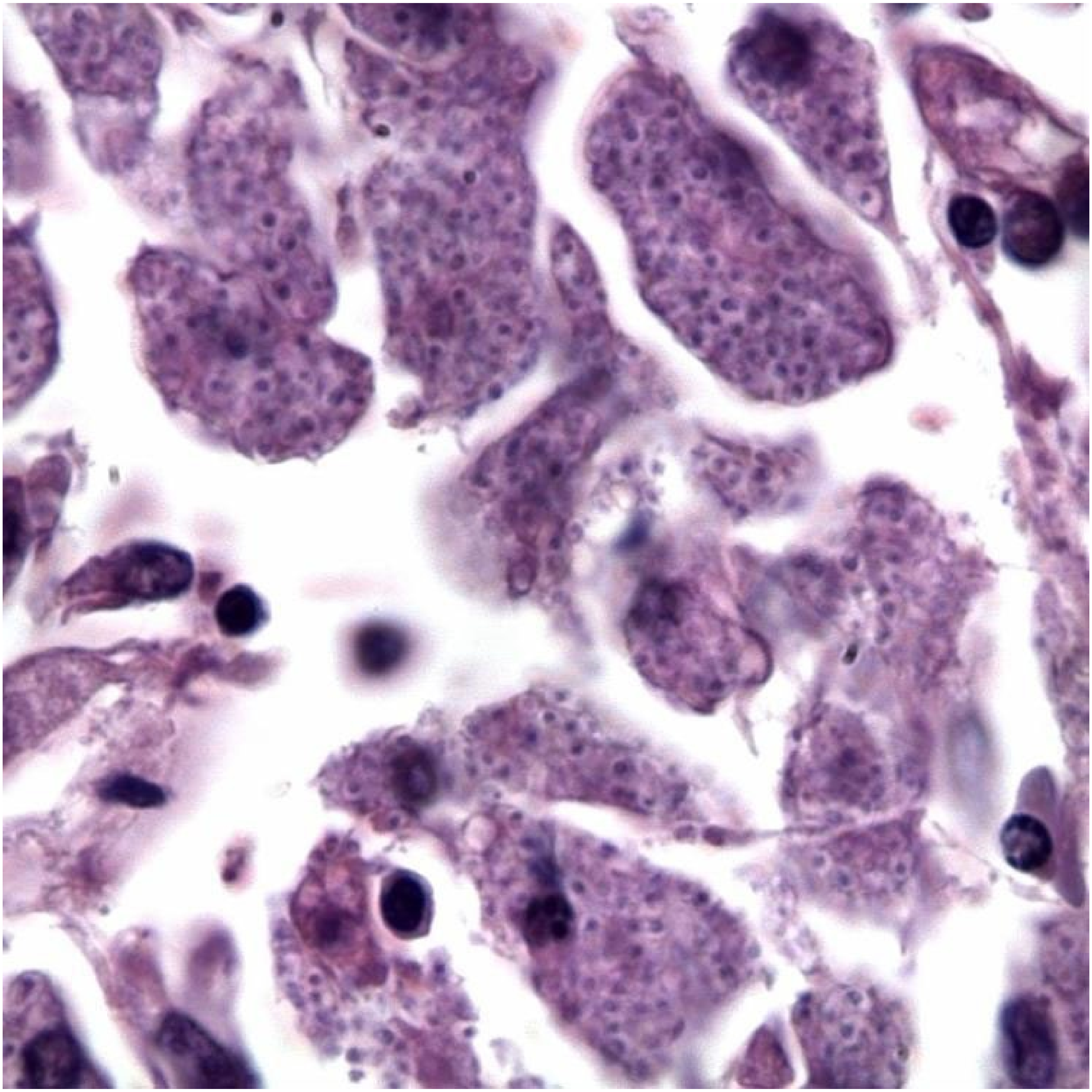
- Sarcoidosis: Similar epithelioid discrete granulomas
- Leishmaniasis: Kinetoplast and GMS negative
- Candidiasis: Larger yeast, more budding
- Penicilliosis: Pill capsule forms; different geographic distribution



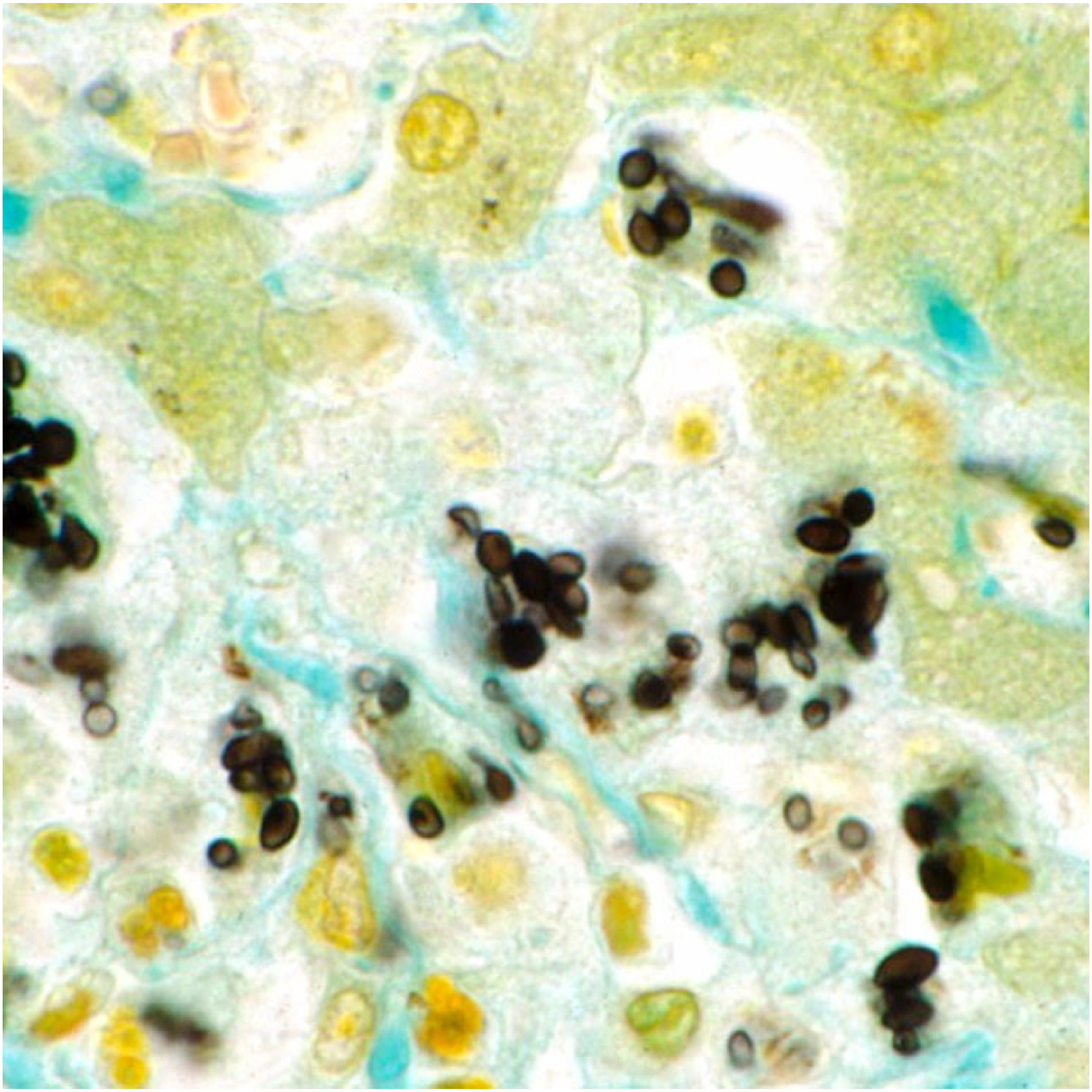
Granulomas
This liver biopsy in a patient with disseminated histoplasmosis contains large, coalescent, epithelioid granulomas.



Lymphohistiocytic Inflammation
Immunocompromised patients with disseminated histoplasmosis may have only necrosis along with lymphocytes and histiocytes that are filled with organisms →, rather than well-formed granulomas.



Intracellular Organisms
This high-power view shows macrophages that are distended with Histoplasma. Note the pale “halo” surrounding the fungi, which is a helpful clue on H&E staining.



GMS, High Power
Histoplasma are uniformly small with narrow-based buds at the more pointed end of the organism.

TERMINOLOGY

Definitions

• Infection by the fungus *Histoplasma capsulatum*

ETIOLOGY/PATHOGENESIS

Histoplasma capsulatum

- Dimorphic fungus
  - Found in soil, particularly when contaminated with bird or bat droppings
- Exists as mycelial form at room temperature and as yeast form at body temperature
- Mechanism of infection
  - Aerosolized microconidia are inhaled
    - Survive within macrophages as yeast form
    - Organism disseminates throughout reticuloendothelial cell system
    - In immunocompetent patients, sensitized T cells activate macrophages, which then are able to kill organism

CLINICAL ISSUES

Epidemiology

- Geographic distribution
  - Variety of endemic areas around globe
  - Ohio, Missouri, and Mississippi River valleys and parts of eastern United States
  - ☐ Most common endemic mycosis in United States
- Central and South America
- Parts of southern Europe, Africa, and southeastern Asia
- Conditions associated with infection/outbreaks
  - Demolition of buildings
  - Moving soil contaminated with bird or bat droppings
  - Uprooting trees where birds roost
  - Spelunking in caves where bats live

Presentation

- Acute disseminated infection
  - Usually occurs in immunosuppressed patients
  - Disseminated histoplasmosis occurs in ~ 55% of infected immunocompromised patients and 4% of infected immunocompetent patients
  - ☐ Liver is involved in up to 90% of cases of disseminated disease
  - ☐ Patients may present with signs of liver/GI involvement rather than pulmonary involvement
- Typically symptomatic
- Chills/fever
- Anorexia/weight loss
- Mucous membrane ulcers
- Skin lesions
- Hepatosplenomegaly
- Elevated liver enzymes

□ Especially alkaline phosphatase
○ Risk factors for disseminated disease
– Exposure in infancy
□ Cell-mediated immunity may not be well developed yet
– HIV/AIDS
□ Particularly if CD4 cell count < 150 cells per µL
– Use of corticosteroids or other immunosuppressive drugs
– Use of tumor necrosis factor antagonists: Etanercept, infliximab, and adalimumab
– Hematologic malignancies
– History of solid organ or bone marrow transplant

- Chronic progressive disseminated infection
  - ○ Typically occurs in older patients without immunosuppression who are unable to control organism
    - – Usually don't have other causes of immunosuppression
      - □ Unable to effectively combat infection, however
  - ○ Presentation: Fever, night sweats, weight loss, fatigue, and oral ulcers are common
    - – Fever
    - – Night sweats
    - – Weight loss
    - – Fatigue
    - – Oral ulcers
    - – Adrenal insufficiency
      - □ Develops as adrenal glands are destroyed by infection
- Reactivation
  - ○ Infection can present as reactivation years after initial exposure if cell mediated immunity is compromised
  - ○ May occur outside of endemic area
- Most infections in immunocompetent persons are self-limited and often clinically unrecognized

Laboratory Tests

- Fungal culture of tissue or blood
  - Serologic antibody assays
  - ○ Complement fixation tests
  - ○ Immunodiffusion assays
  - ○ Not useful in some circumstances
  - – Patients with acute disseminated infection who might not have developed antibody yet
  - – Immunocompromised patients, elderly patients, and very young children who may not be able to make antibody
- Antigen detection assays
  - ○ Enzyme immunoassay

- High sensitivity (80-90%)
- Can be used on urine, serum, or other body fluid samples
- PCR tests
  - Can be performed on fresh samples as well as formalin fixed, paraffin embedded tissue

Treatment

- Drugs
  - Antifungal agents: Itraconazole, amphotericin B

Prognosis

- With treatment, mortality rate is < 10%
- Immunocompromised patients have worse prognosis than immunocompetent patients

MACROSCOPIC

General Features

- Enlarged liver appears congested or mottled
- Infection may produce nodules up to 1 cm in diameter

MICROSCOPIC

Histologic Features

- Portal and lobular lymphohistiocytic inflammation
  - May be limited or virtually no inflammatory response in severely immunocompromised patients
- Discrete granulomas in portal and lobular regions can be seen regardless of immune status
  - Well-formed granulomas often absent in immunocompromised patients
- Kupffer cell hyperplasia
- Large numbers of fungi often present in portal and sinusoidal macrophages
- Infection may produce discrete nodules containing caseous necrotic material with histocytic or fibroblastic rim
  - As nodules age, may become entirely fibrotic with calcifications
- Characteristics of organism
  - Uniformly small (2-4 µm)
  - Oval with narrow-based bud at more pointed pole
  - May have surrounding pale "halo" on H&E and PAS stains
  - Typically intracellular (within macrophages)

ANCILLARY TESTS

Histochemistry

- GMS
- PAS diastase

DIFFERENTIAL DIAGNOSIS

Pneumocystosis

- Similar in size
- Extracellular
- Lack of budding
- Characteristic internal structure
- Foamy cast appearance of inflammatory reaction

Candidiasis

- Slightly larger
- Extracellular
- More frequent budding

Cryptococcosis

- Pleomorphic in size rather than uniformly small
- Often mucicarmine-positive capsule
- Positive with Fontana-Masson stain

Leishmaniasis

- Presence of kinetoplast
- GMS negative

Penicilliosis

- May be similar in size
- Different endemic area (Southeast Asia)
- Elongated and septate (pill capsule) forms as well as small budding yeast

Sarcoidosis

- May be indistinguishable from histoplasmosis by morphology alone
- Different clinical context

DIAGNOSTIC CHECKLIST

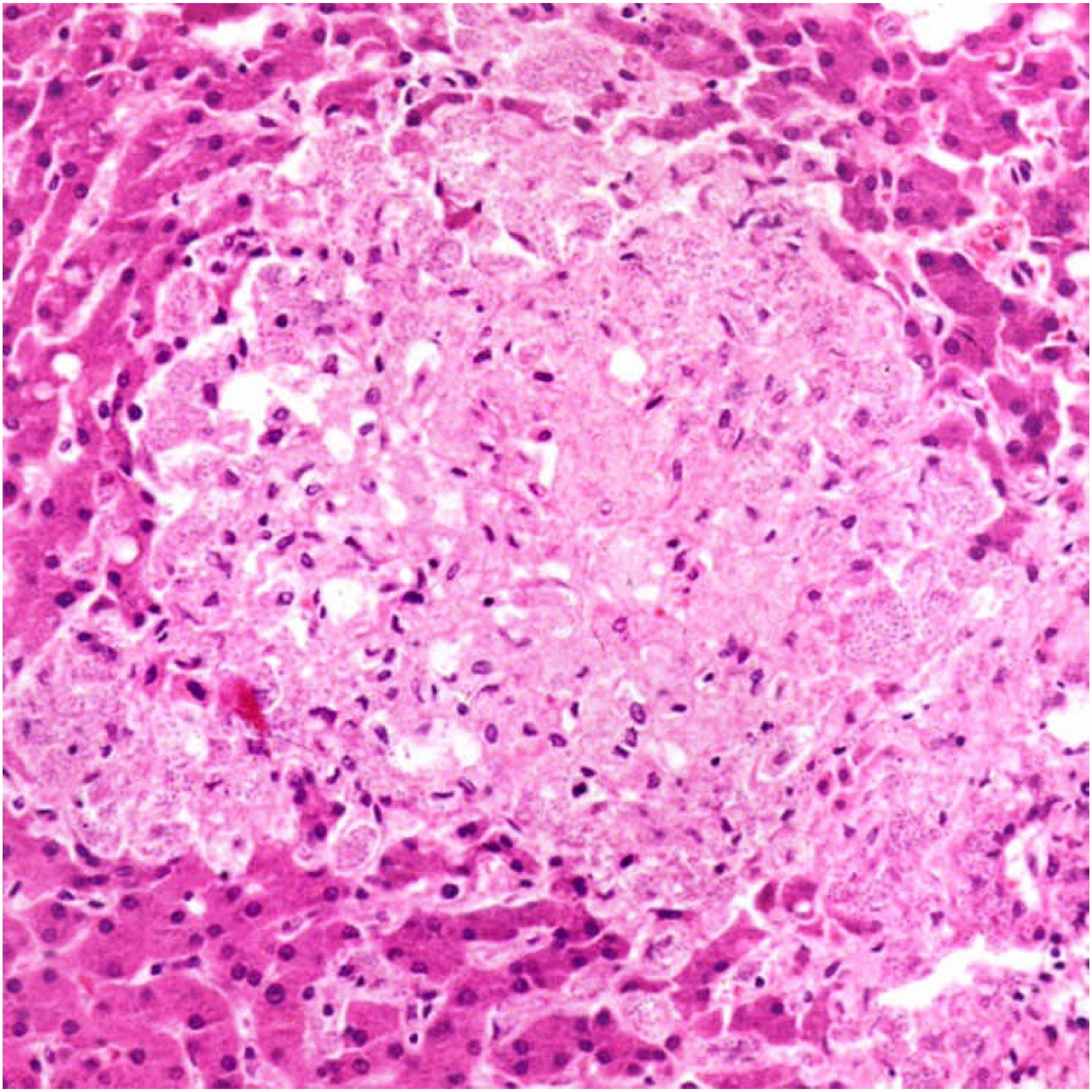
Clinically Relevant Pathologic Features

- Liver is involved in up to 90% of cases of disseminated disease

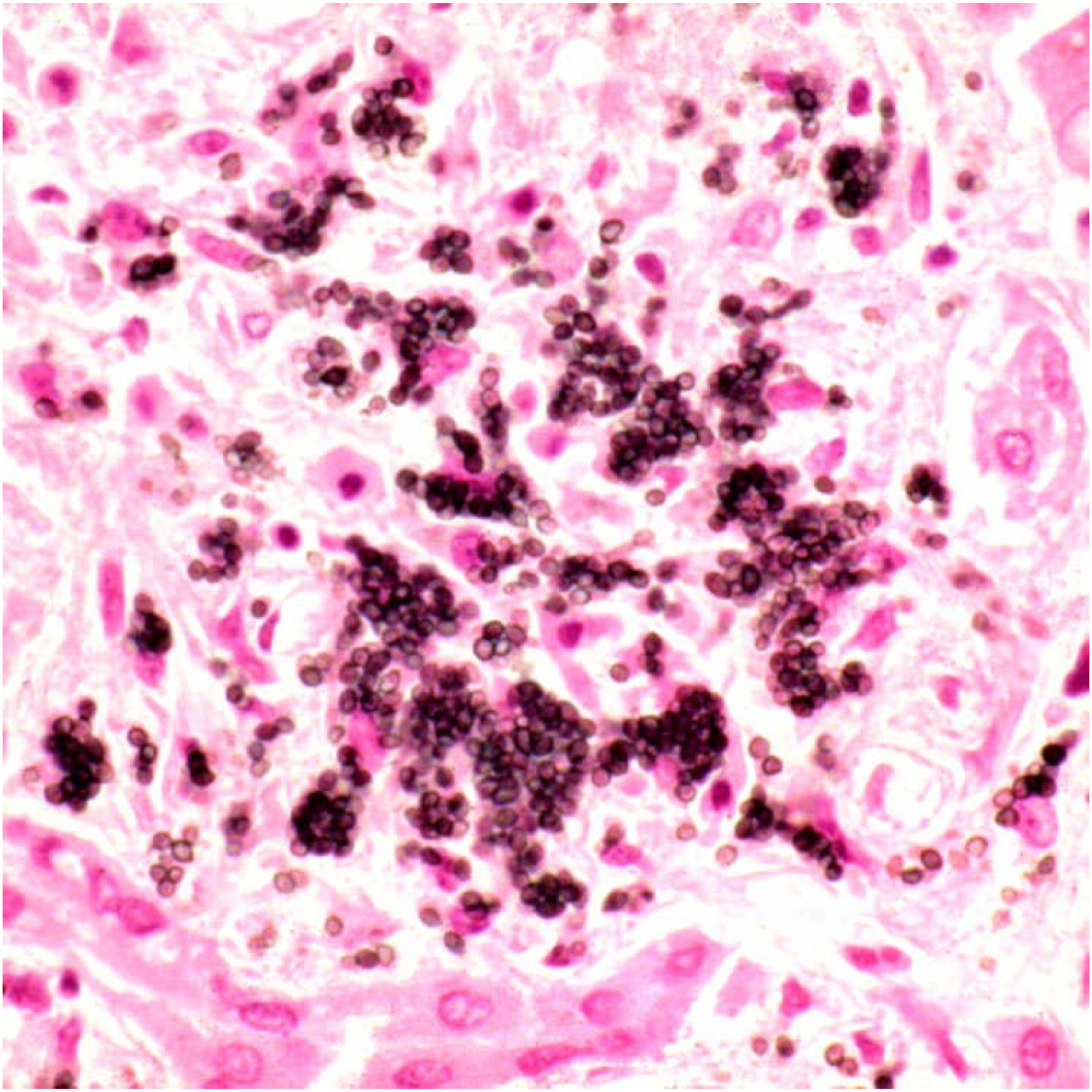
• Patients may present with symptoms/signs of liver involvement rather than pulmonary involvement

Pathologic Interpretation Pearls

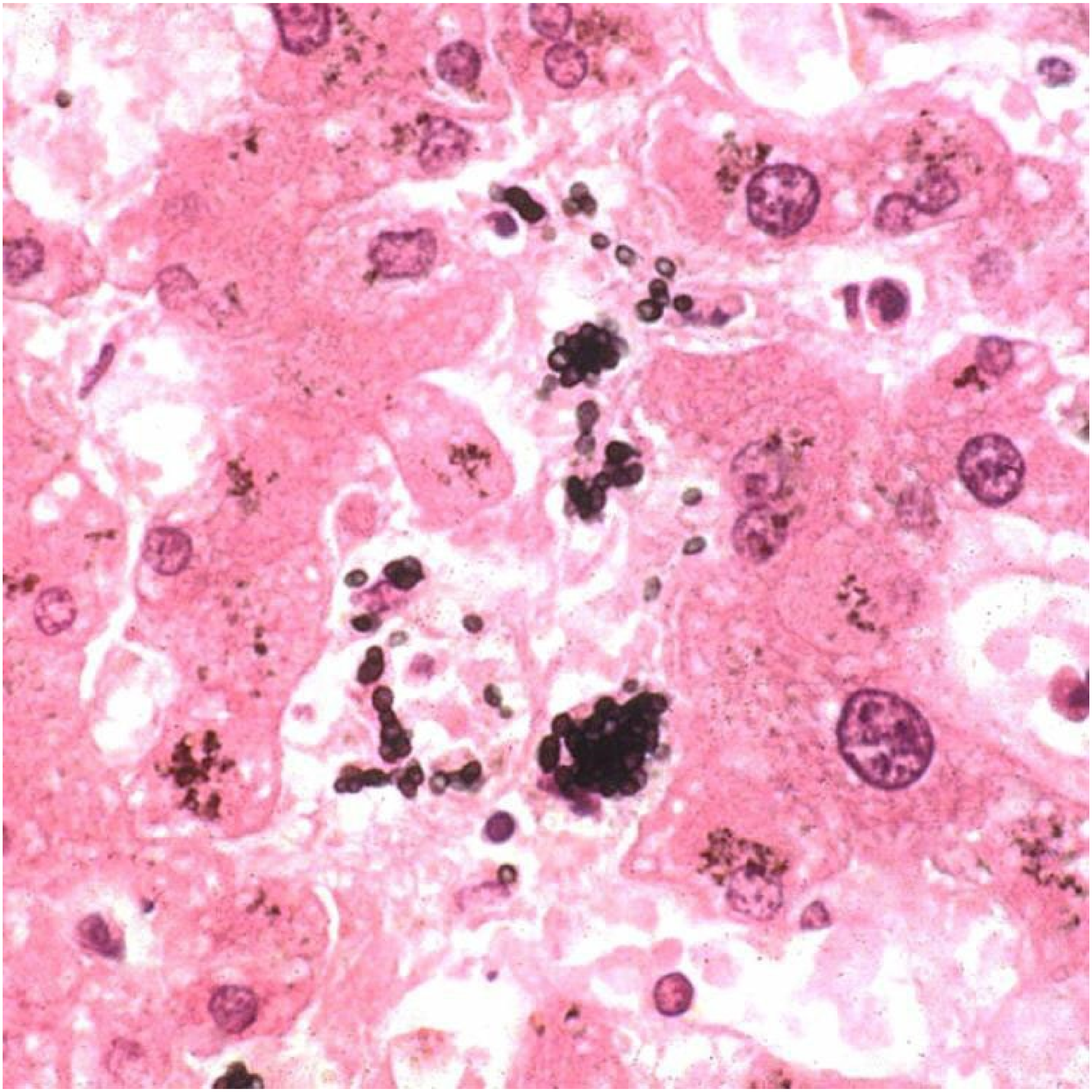
• Liver biopsies may show little inflammation in immunocompromised patients, so liberal use of special stains is warranted



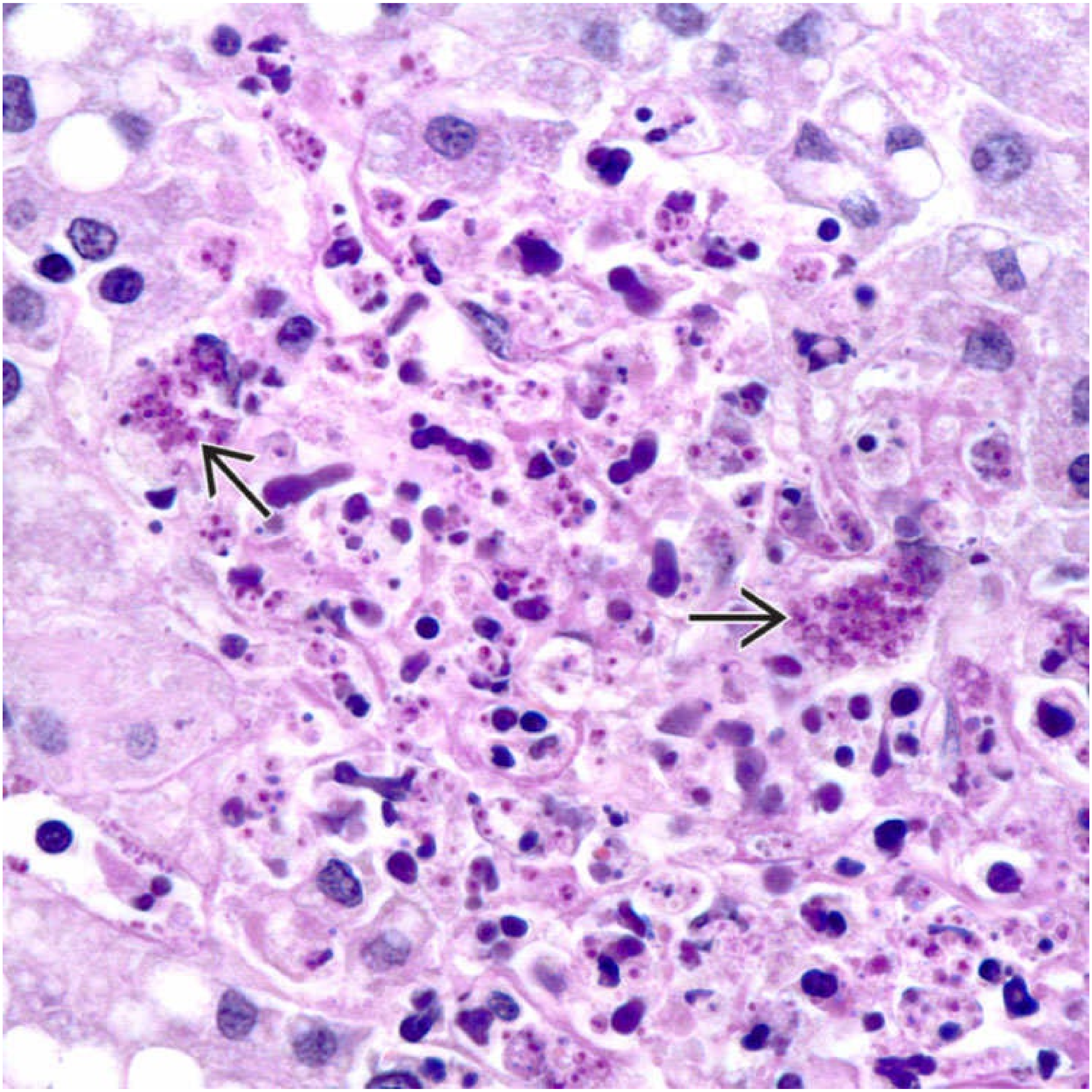
Macrophage Clusters
In this example of disseminated histoplasmosis in a severely immunocompromised patient, clusters of histiocytes are present in the lobule, with minimal associated inflammation.



H&E/GMS Stain
A methenamine silver with H&E counterstain nicely demonstrates the yeast within a collection of portal macrophages in the liver. There is minimal associated inflammation in this severely immunocompromised patient.

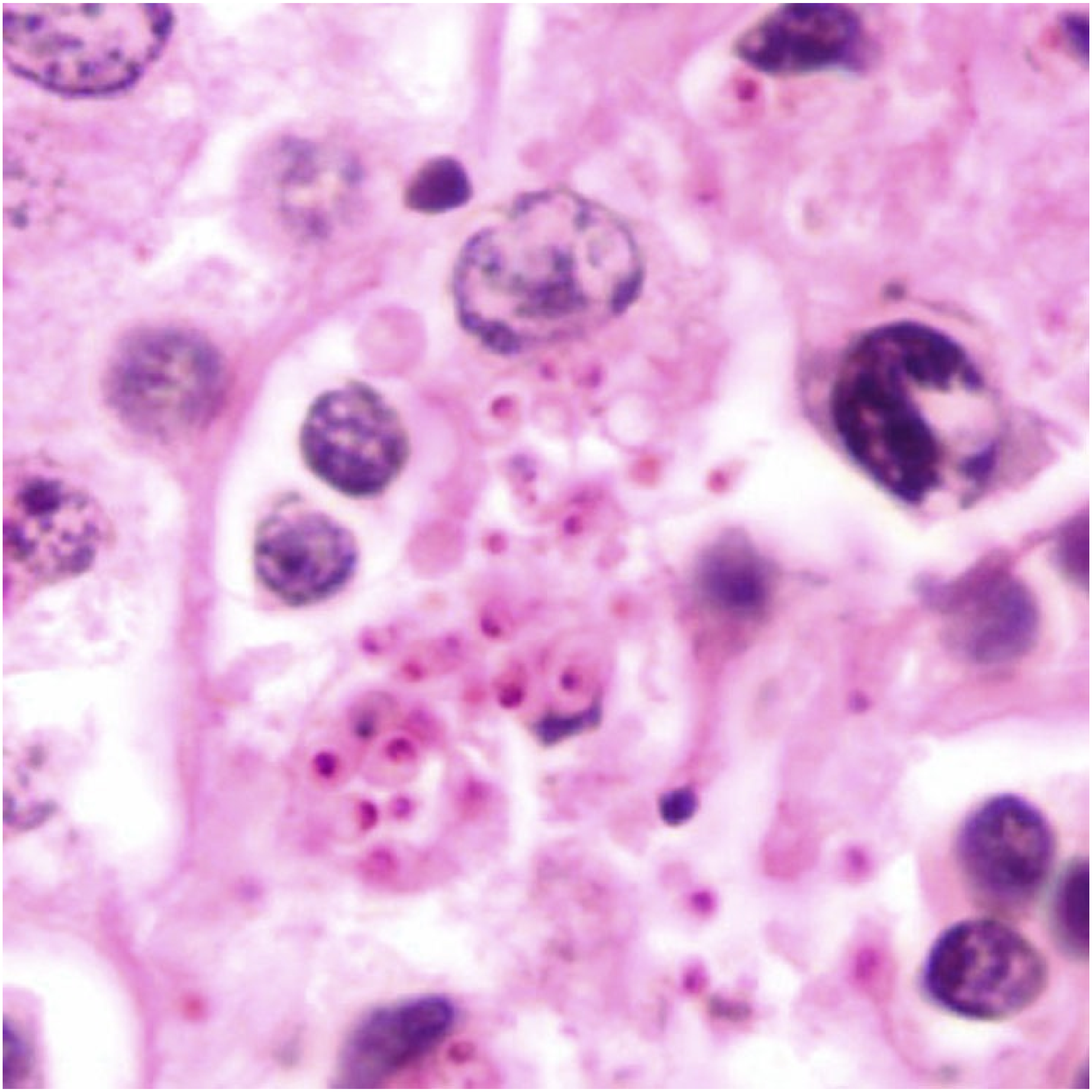


Yeast in Sinusoidal Macrophages
A high-power view of methenamine silver stain with H&E counterstain shows small budding yeast within sinusoidal macrophages.

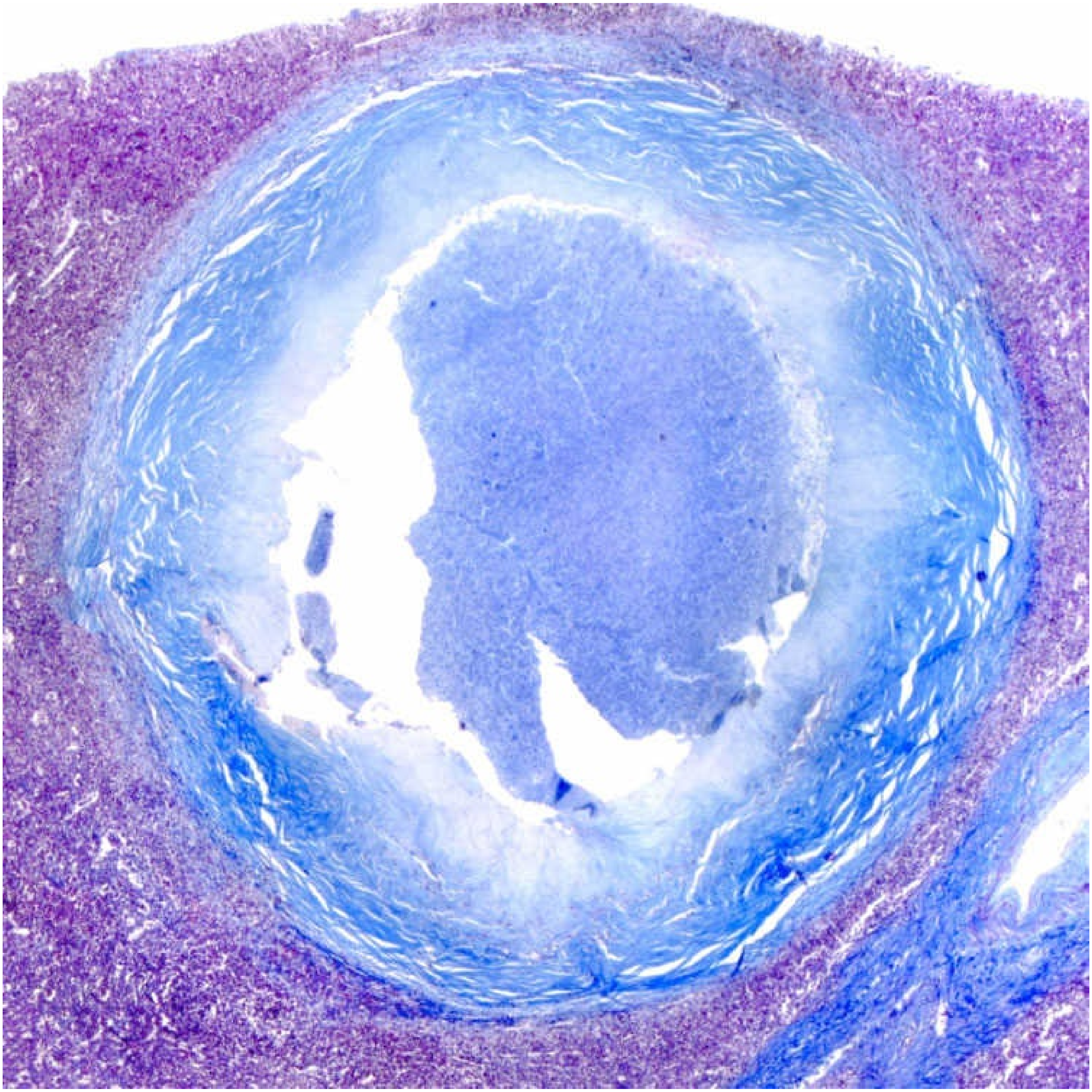


PAS-Diastase

PAS-diastase stain of a liver biopsy shows macrophages filled with yeast → in the necrotic foci.



PAS-Diastase, High Magnification
PAS diastase stain at very high magnification shows macrophages with numerous intracellular yeast that appear as small oval organisms with a distinctive “halo” effect. This is typical of histoplasmosis.



Fibrotic Granuloma
A fibrotic granuloma with central necrosis is present in a patient with hepatosplenic histoplasmosis.

SELECTED REFERENCES

1. Rihana, NA, et al. Histoplasmosis presenting as granulomatous hepatitis: case report and review of the literature. *Case Rep Med*. 2014; 2014:879535.
2. Assi, M, et al. Histoplasmosis after solid organ transplant. *Clin Infect Dis*. 2013; 57(11):1542–1549.
3. Koepsell, SA, et al. Applying a real-time PCR assay for Histoplasma capsulatum to clinically relevant formalin-fixed paraffin-embedded human tissue. *J Clin Microbiol*. 2012; 50(10):3395–3397.
4. Kauffman, CA. Histoplasmosis. *Clin Chest Med*. 2009; 30(2):217–225. [v].

5. Huber, F, et al. AIDS-related Histoplasma capsulatum var. capsulatum infection: 25 years experience of French Guiana. *AIDS*. 2008; 22(9):1047–1053.
6. Lamps, LW, et al. The pathologic spectrum of gastrointestinal and hepatic histoplasmosis. *Am J Clin Pathol*. 2000; 113(1):64–72.
7. Collins, MH, et al. Hepatic granulomas in children. A clinicopathologic analysis of 23 cases including polymerase chain reaction for histoplasma. *Am J Surg Pathol*. 1996; 20(3):332–338.

Cryptococcosis

KEY FACTS

Terminology

- Infection by fungi *Cryptococcus neoformans* or *Cryptococcus gattii*
  - Most common cause of systemic mycosis in patients with AIDS
    - Liver involvement is usually feature of disseminated disease
    - Most common in, but not limited to, immunocompromised patients

Etiology/Pathogenesis

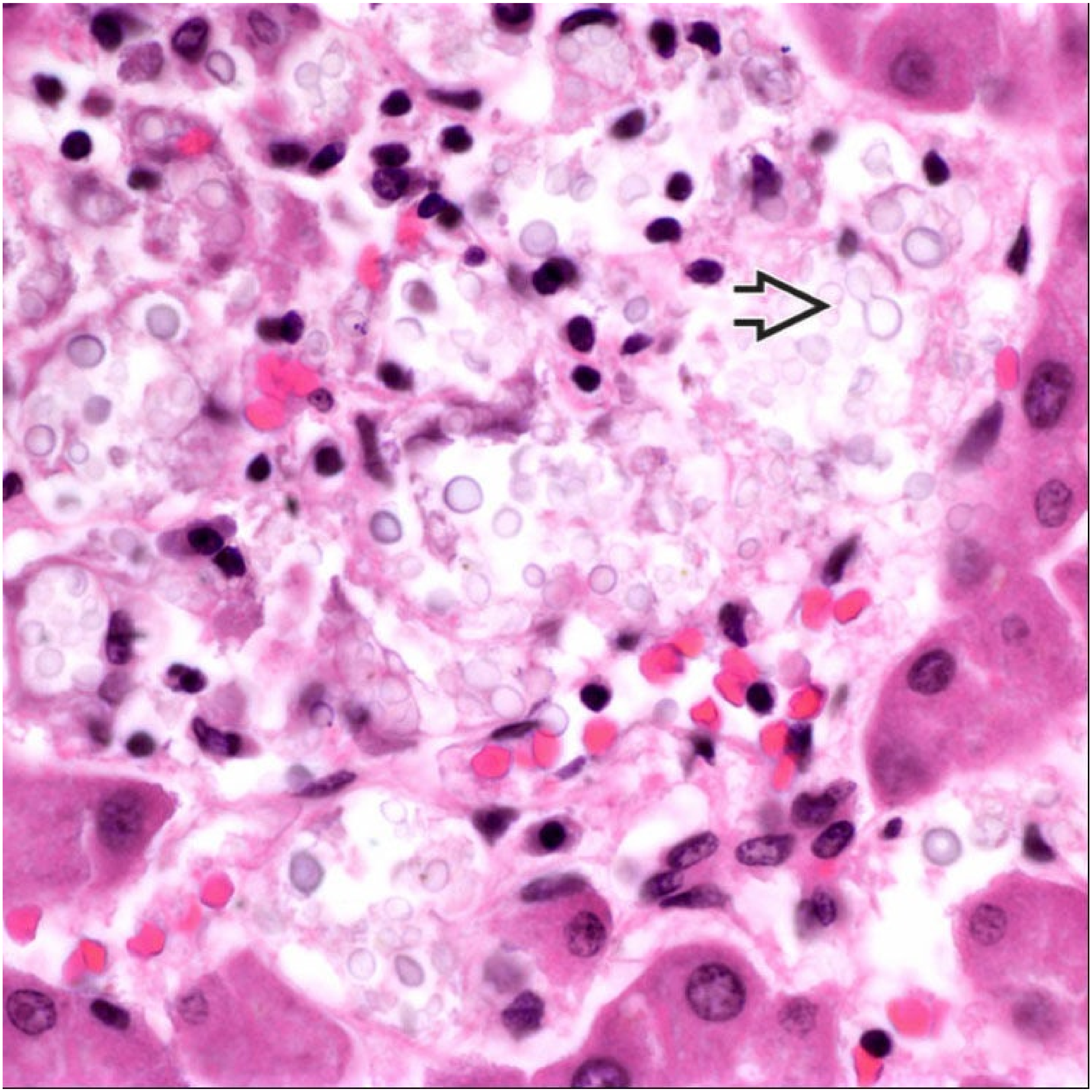
- Worldwide distribution and widespread in nature
- Ubiquitous soil saprophyte; acquired by inhalation

Clinical Issues

- Liver involvement often presents as hepatomegaly, abdominal pain, elevated liver tests
  - Helpful laboratory tests include culture, cryptococcal antigen testing, and PCR assays
  - Prognosis depends on clinical features of disease, patient's immune status
    - Untreated disease is almost always fatal

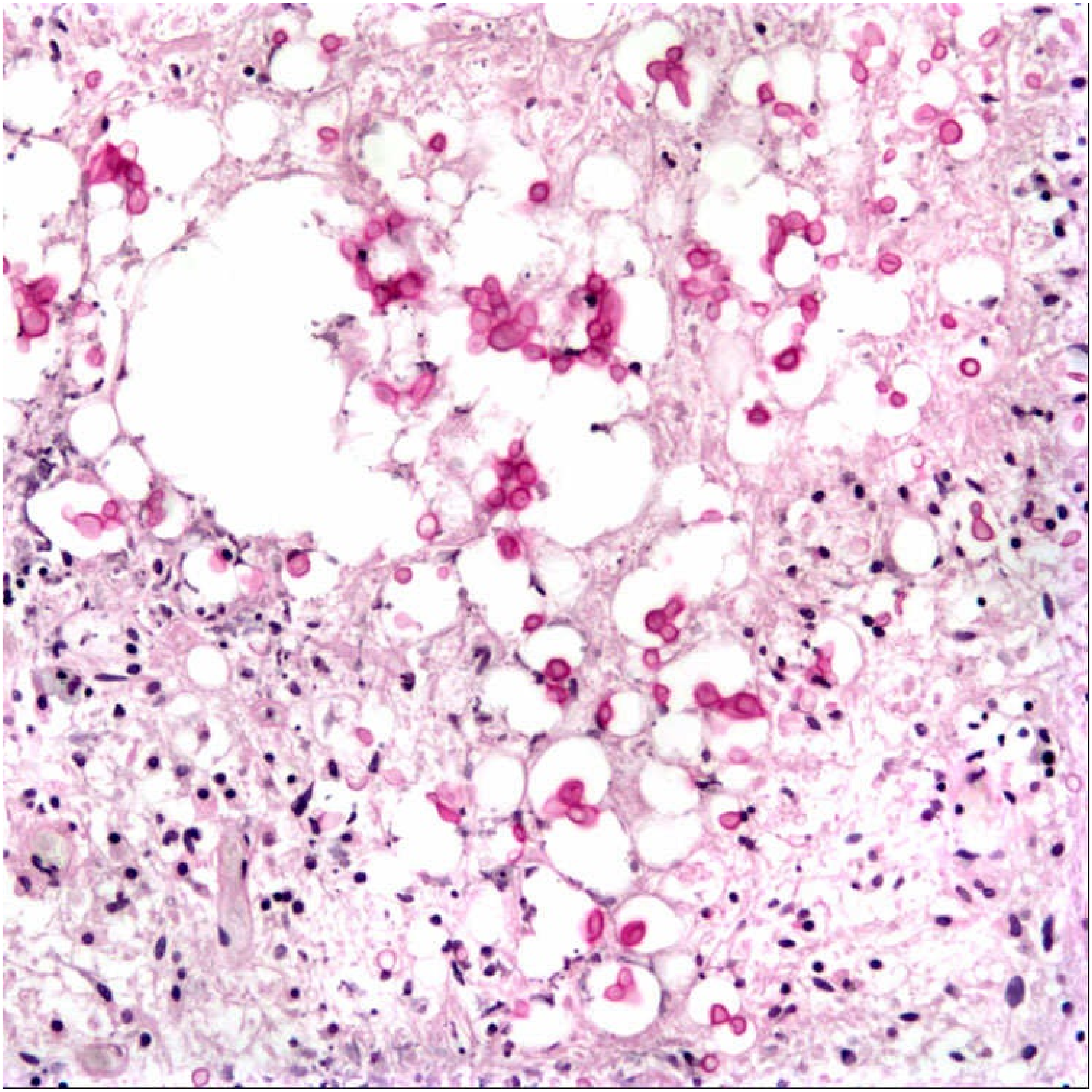
Microscopic

- Round to oval yeast with narrow-based budding
  - Considerable variation in size from 2-20 µm in diameter
  - Halo around organisms representing mucopolysaccharide capsule
  - Variable inflammatory response
    - Ranges from suppurative &/or granulomatous inflammation to essentially no tissue reaction in severely immunocompromised patients
- Fungi stain with GMS, Alcian blue, mucicarmine, colloidal iron, and Fontana-Masson
- Capsule deficient organisms are mucicarmine negative or only weakly positive
  - Fontana-Masson is useful in these cases



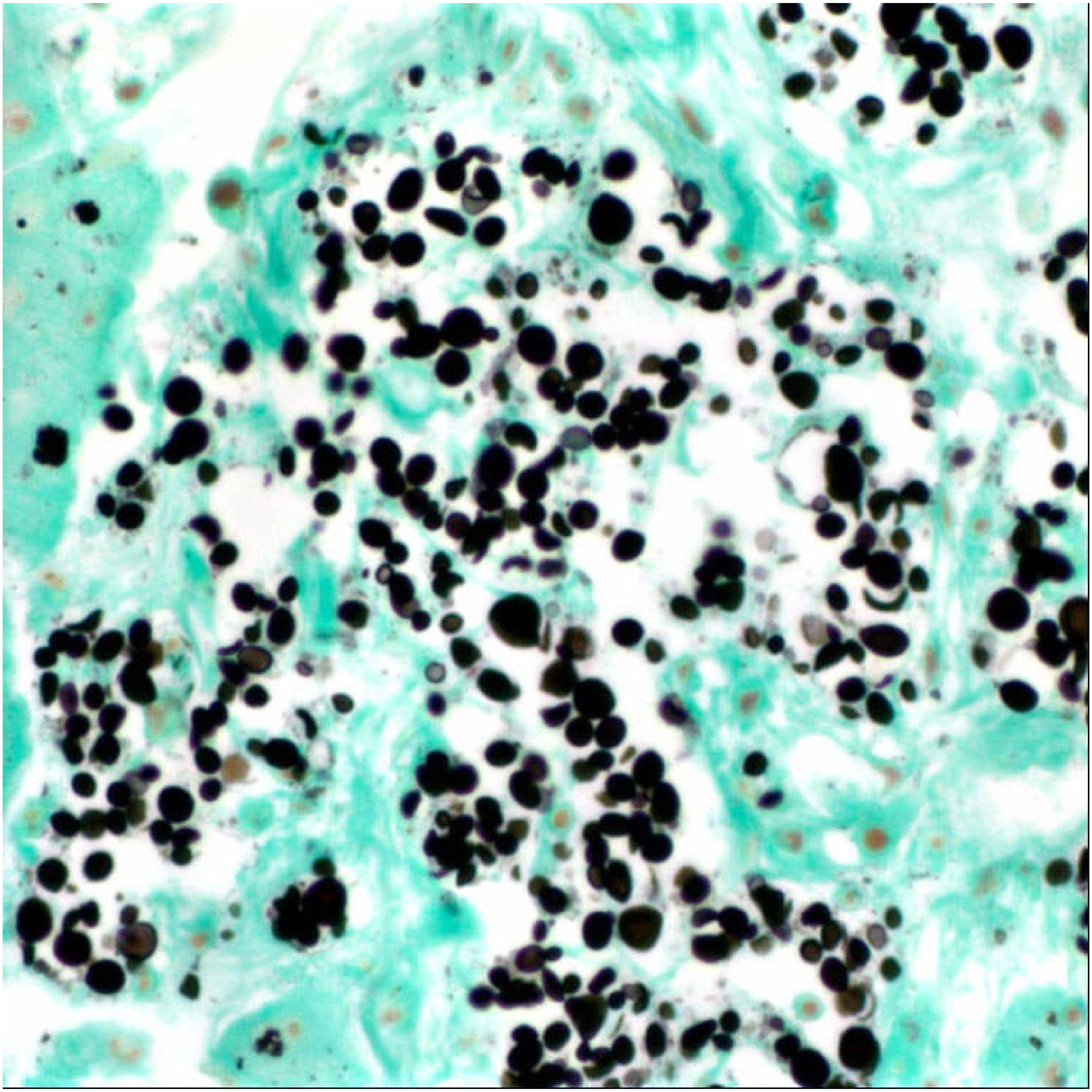
Narrow-Based Budding

This liver biopsy shows numerous cryptococci expanding the hepatic sinusoids. Note the narrow-based bud and the variation in size. There is minimal inflammatory reaction in this immunocompromised patient.



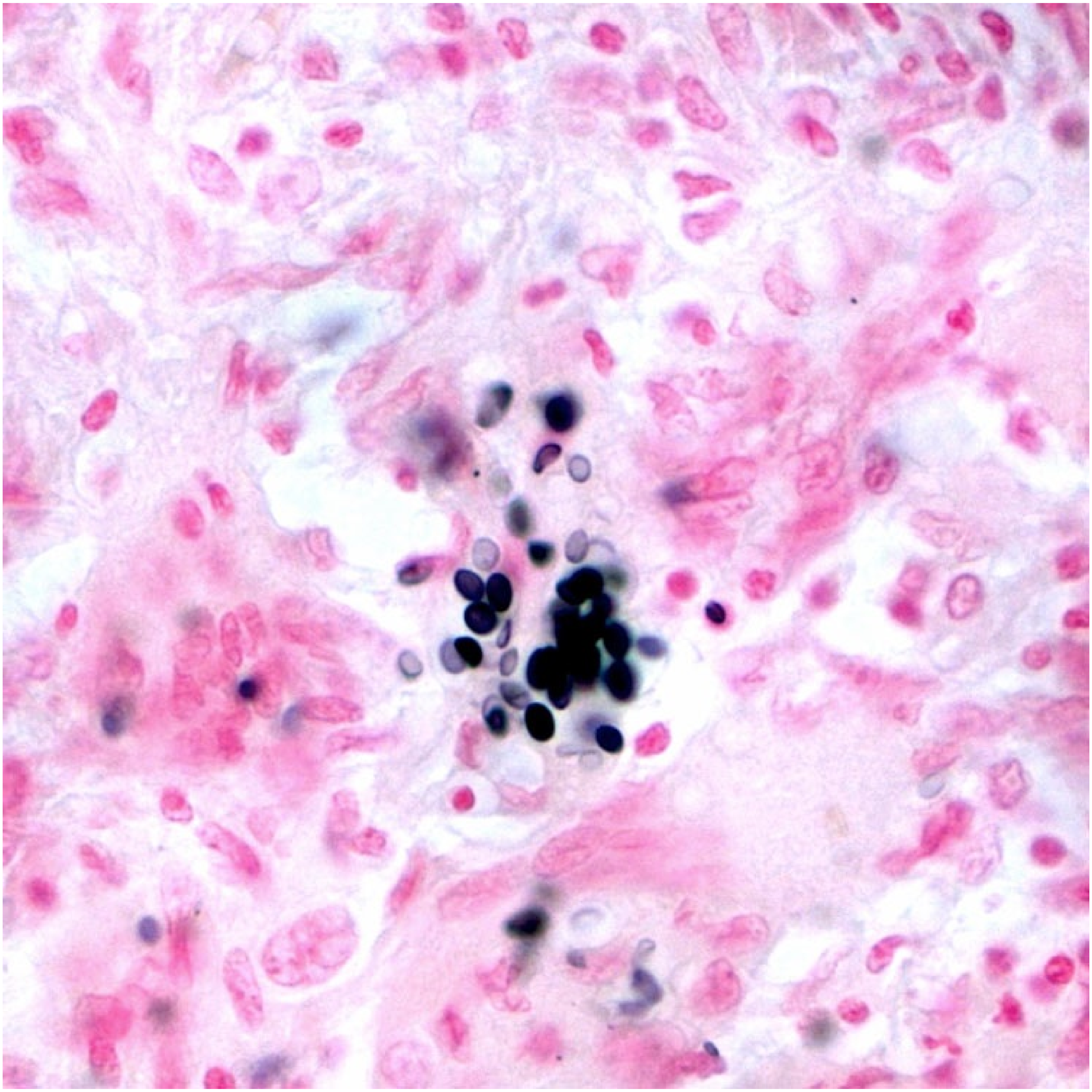
Mucicarmine Stain

Mucicarmine stain highlights the mucopolysaccharide capsule characteristic of Cryptococcus. However, many Cryptococcus strains are capsule deficient, and may be negative for mucicarmine or only weakly positive. (Courtesy B. Smoller, MD.)



GMS Stain

Gomori methenamine silver stain highlights the pleomorphic size of Cryptococcus. This slide shows the presence of both small and large organisms.



Fontana-Masson Stain
Fontana-Masson will stain the fungi black in Cryptococcus infection, including capsule-deficient fungi, due to the melanin in the cell wall.

TERMINOLOGY

Synonyms

- Cryptococcosis

Definitions

- Infection by fungi *Cryptococcus neoformans* or *Cryptococcus g attii*

- *C. gattii* more common in immunocompetent persons
- Most common cause of systemic mycosis in patients with AIDS
- Liver involvement is often part of disseminated disease with multisystem organ involvement

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Worldwide distribution and widespread in nature
  - Ubiquitous soil saprophyte; acquired by inhalation
  - Most abundant in avian habitats, especially those with pigeon or chicken excreta

CLINICAL ISSUES

Presentation

- Most often encountered as opportunistic infection in immunosuppressed patients (AIDS, transplant patient, malignancy, corticosteroid therapy, etc.)
  - Hepatomegaly, abdominal pain, elevated liver tests indicate liver involvement

Laboratory Tests

- Culture
  - Cryptococcal antigen testing on serum or CSF
  - Patients with low fungus burden or capsule deficient infection may have false-negative result
- PCR

Treatment

- Drugs
  - Antifungal drugs are mainstay of therapy

Prognosis

- Depends on clinical features of disease, patient’s immune status
- Untreated disease is almost always fatal

MACROSCOPIC

General Features

- Usually unremarkable; rarely there are multiple foci of necrosis
- Extrahepatic biliary tree may be involved, mimicking sclerosing cholangitis

MICROSCOPIC

Histologic Features

- Fungal morphology
  - Round to oval yeast
  - Narrow-based buds
  - Considerable variation in size, ranging from 2-20 μm in diameter
  - Halo around organisms representing mucopolysaccharide capsule
  - – Soap bubble appearance at low magnification
  - – Capsule may have diameter up to 5x that of fungal cells they surround
- Occasionally may produce hyphae and pseudohyphae
- Variable inflammatory response
  - Usually minimal accompanying inflammation, especially in immunocompromised patients
    - – Kupffer cells or portal macrophages contain engulfed yeast
  - May have suppurative, granulomatous, or mixed tissue reaction
  - Occasionally large multinucleated giant cells containing yeast are present
- Histochemical stains
  - GMS positive
  - Capsule will stain with Alcian blue, mucicarmine, colloidal iron, and Fontana-Masson
    - – Capsule deficient organisms are mucicarmine negative or only weakly positive, making diagnosis more difficult; Fontana-Masson is useful in these cases

DIFFERENTIAL DIAGNOSIS

Other Fungal Infections

- *Blastomyces dermatitidis*
  - Larger and more uniform in size than *Cryptococcus*
  - Broad-based buds
  - Occasionally mucicarmine positive, but negative on Fontana-Masson
- *Histoplasma capsulatum*
  - Smaller and more uniform in size than *Cryptococcus*
  - Mucicarmine and Fontana-Masson negative

Other Suppurative and Granulomatous Processes

- Bacterial and mycobacterial infections
- Noninfectious causes of hepatic granulomas

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Often represents part of a disseminated infection

- Patients are usually immunocompromised

Pathologic Interpretation Pearls

- Mucin-positive capsule is highly suggestive of *Cryptococcus* species
    - Negative mucicarmine stain does not exclude cryptococcosis
- Capsule-deficient *Cryptococcus* often has at least some weakly positive cells when mucin stains are examined carefully

SELECTED REFERENCES

1. Patel, NC, et al. Disseminated Cryptococcus neoformans: case report and review of the literature. *Cutis*. 2009; 84(2):93–96.
2. Lazcano, O, et al. Combined histochemical stains in the differential diagnosis of Cryptococcus neoformans. *Mod Pathol*. 1993; 6(1):80–84.
3. Bonacini, M, et al. Gastrointestinal, hepatic, and pancreatic involvement with Cryptococcus neoformans in AIDS. *J Clin Gastroenterol*. 1990; 12(3):295–297.
4. Kovacs, JA, et al. Cryptococcosis in the acquired immunodeficiency syndrome. *Ann Intern Med*. 1985; 103(4):533–538.
5. Sabesin, SM, et al. Hepatic failure as a manifestation of cryptococcosis. *Arch Intern Med*. 1963; 111:661–669.

Amebiasis

KEY FACTS

Terminology

- Infection of liver by protozoa *Entamoeba histolytica*

Etiology/Pathogenesis

- Risk factors for infection
  - Poor sanitation, exposure to contaminated water
  - Sexual or fecal/oral transmission
  - – Men having sex with men have higher incidence than general population
- Liver abscess is most frequent complication of invasive amebiasis

Clinical Issues

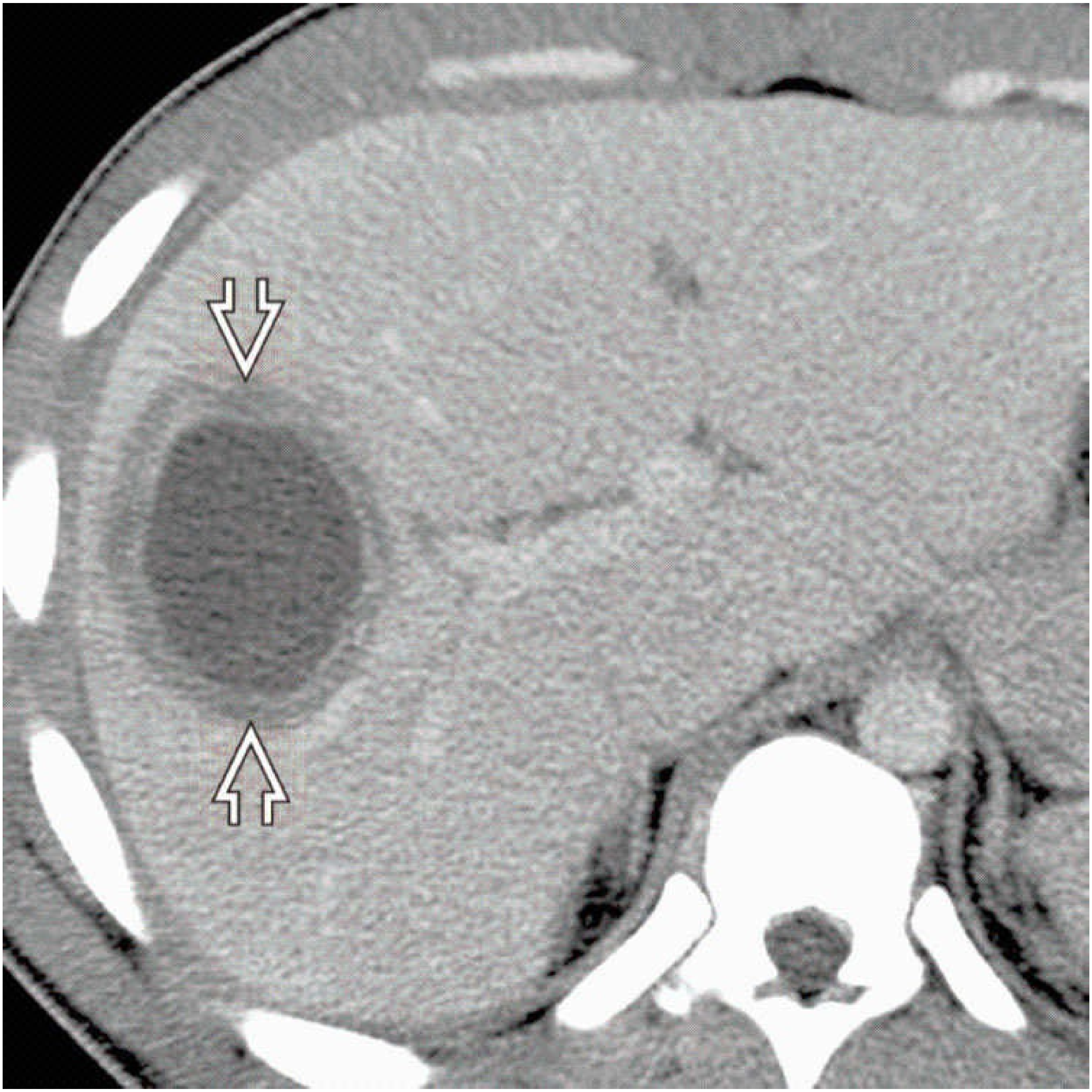
- Fever, sweats, and right upper quadrant pain
  - Hepatomegaly, abdominal tenderness
  - Elevated alkaline phosphatase, leukocytosis common
  - Lab tests
  - Serologic studies, PCR, stool examination
  - – Stool exam cannot distinguish between *E. histolytica* and nonpathogenic ameba
- Treatment
  - Amebicides
  - Guided percutaneous drainage may be required for liver abscess

Macroscopic

- Solitary or multiple lesions, often irregularly shaped, ranging from barely visible to > 20 cm
  - Usually right lobe
  - Often contain necrosis resembling anchovy paste

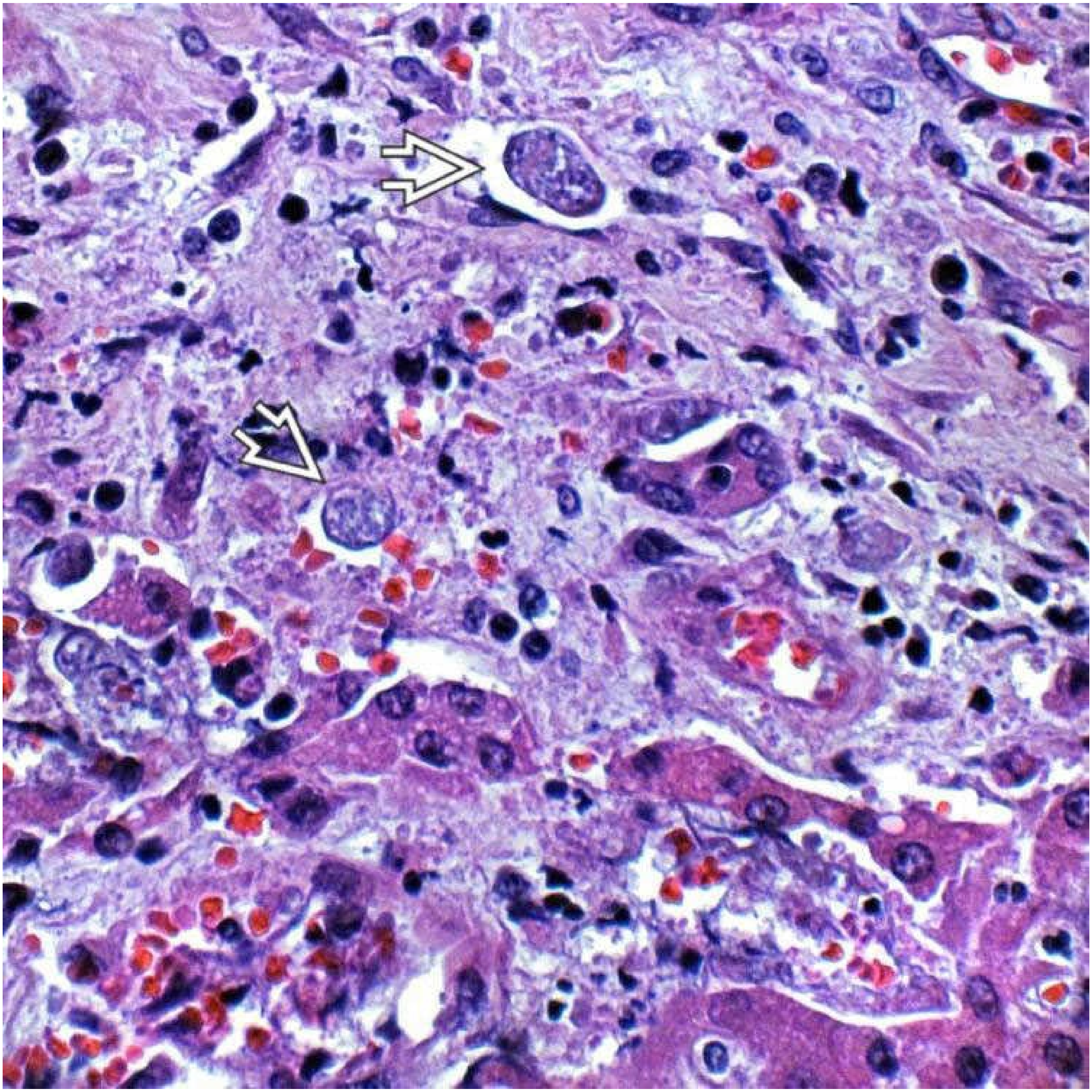
Microscopic

- Abundant nuclear debris but few intact inflammatory cells
  - Organisms have foamy cytoplasm; round, eccentric nuclei
  - Ingested red blood cells essentially pathognomonic of *E. histolytica*
- Trophozoites may mimic macrophages



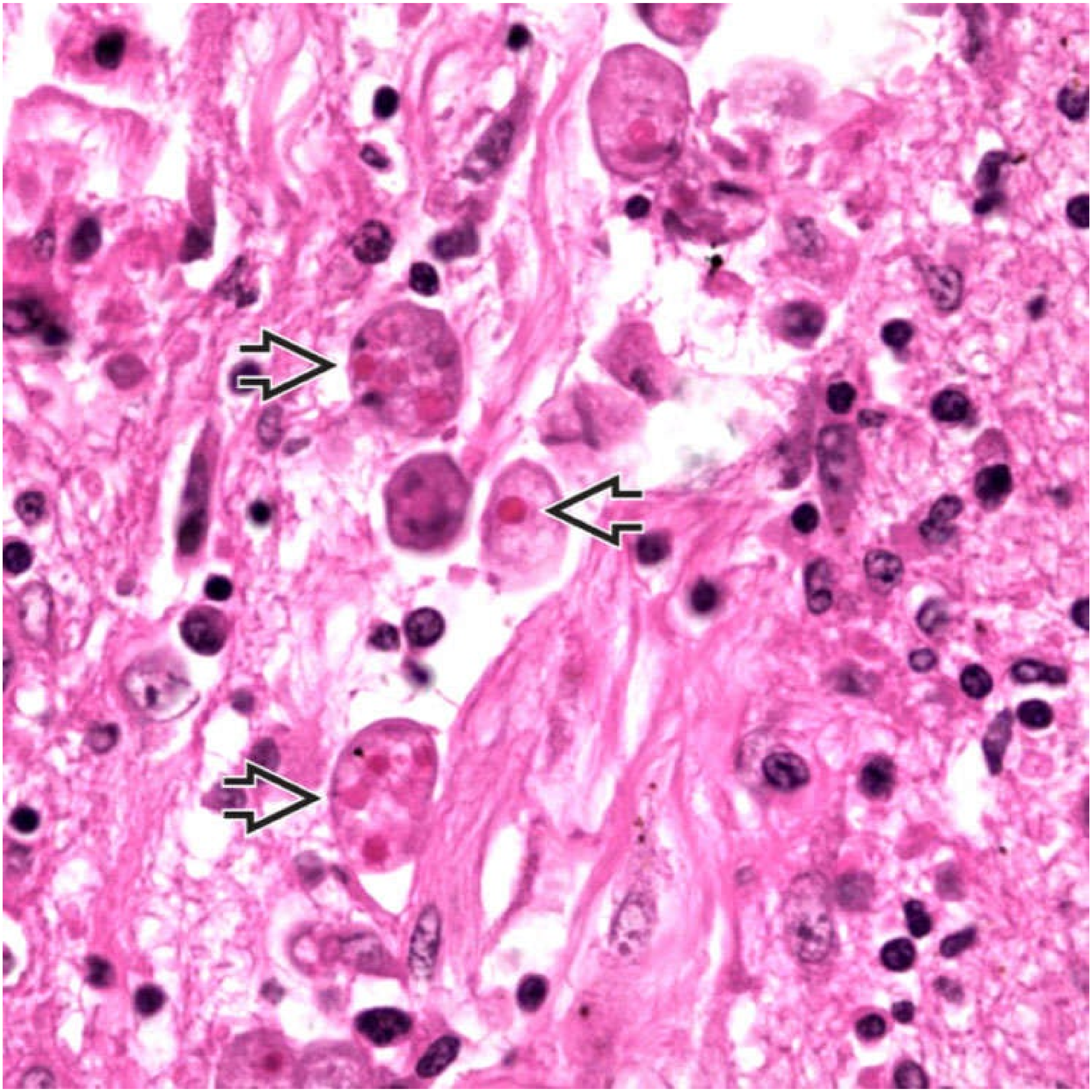
CT Scan

A contrast-enhanced CT of the liver shows an amebic abscess with a surrounding rim ⇨. This cavity was filled with thick, tenacious necrotic debris (anchovy paste).



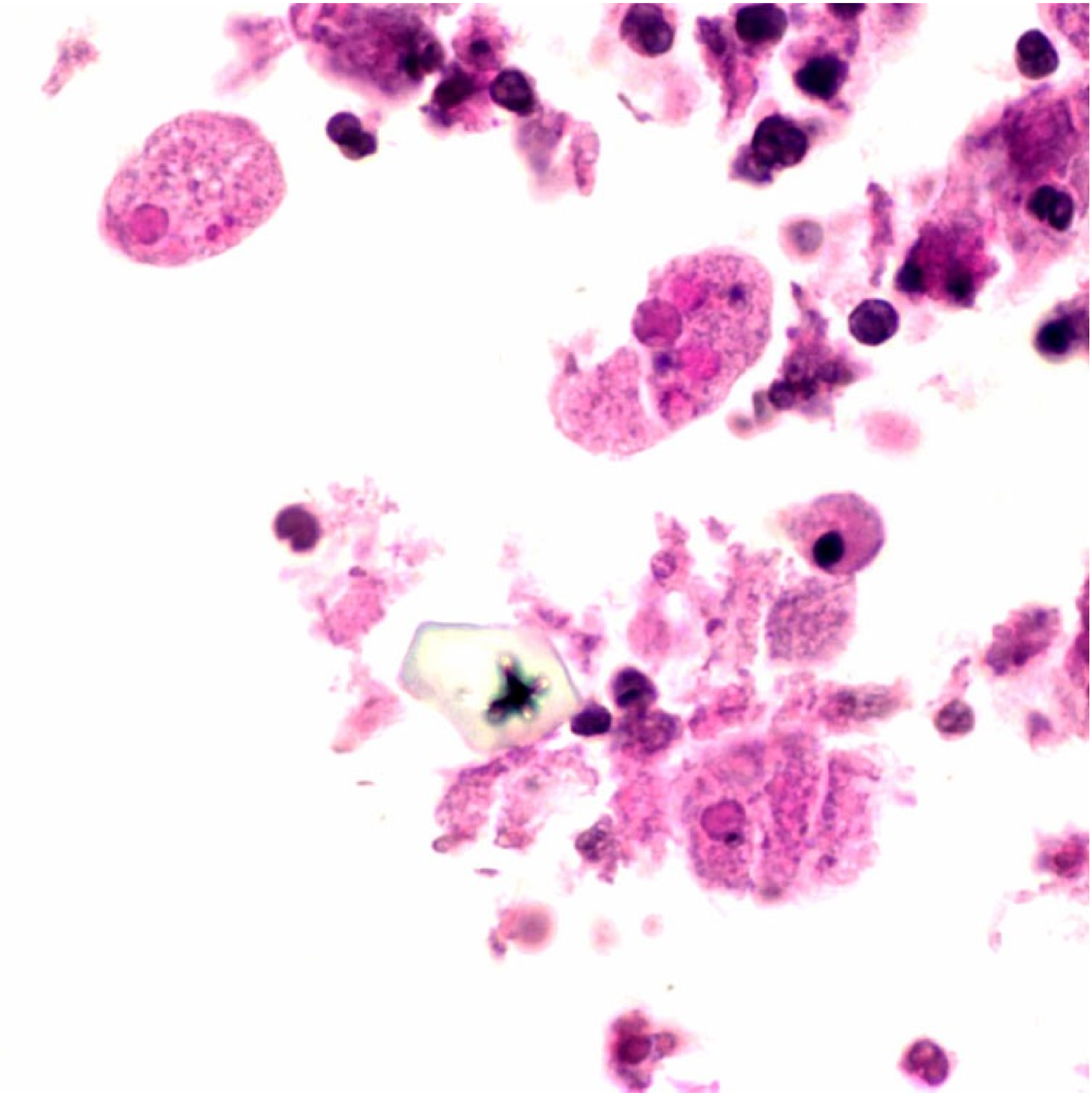
Amebic Liver Abscess

Entamoeba histolytica ⇨ with associated fibrous tissue is shown, but relatively few mononuclear cells are seen at the edge of a liver abscess. Note the residual liver at the bottom 1/2 of the image. (Courtesy Dr. J.C. Garces.)



Ingested Erythrocytes

Ingested red blood cells within the organisms are virtually pathognomonic of E. histolytica ⇨. A sparse mononuclear cell infiltrate is also present.



Features of Organism
High-power view of amebic trophozoites shows the distinct cell membrane, foamy cytoplasm, and round, eccentric nucleus with open chromatin pattern.

TERMINOLOGY

Synonyms

- *Entamoeba histolytica;* amebiasis *;* entamebiasis

Definitions

- Infection of liver by protozoa *E. histolytica*

- Humans are only known reservoir

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Poor sanitation, exposure to contaminated water
  - Most common in poor communities with inadequate sanitation
- Sexual or fecal/oral transmission
  - Men who have sex with men have higher incidence than general population

CLINICAL ISSUES

Epidemiology

- ~ 50 million cases of amebiasis/year occur worldwide
  - Liver abscess is most frequent complication of invasive amebiasis
  - – Portal vein is major route by which ameba get from intestine to liver

Presentation

- Fever with afternoon and night sweats
  - Right upper quadrant pain radiating to scapular region/shoulder
  - Hepatomegaly, abdominal tenderness
  - Malaise, weight loss
  - Jaundice (rare)
  - Complications
  - Rupture of abscess into peritoneum
  - Fistulize with other organs or skin
- Many patients with amebic liver abscess do not have gastrointestinal symptoms

Laboratory Tests

- Elevated alkaline phosphatase in > 50%
  - Elevated transaminases (rare)
  - Leukocytosis in > 90%
  - Serologic testing
  - Highly sensitive and specific
- PCR
- Stool examination
  - Does not distinguish pathogenic from nonpathogenic ameba

Treatment

- Drugs
  - Amebicides
- Guided percutaneous drainage if response to drugs is inadequate, there is bacterial superinfection, or

concern for rupture

Prognosis

- Excellent with modern amebicidal therapy
  - Mortality increases with lack of therapy, dissemination

MACROSCOPIC

General Features

- Solitary or multiple lesions, often irregularly shaped, ranging from barely visible to > 20 cm
  - Usually right lobe
- May have prominent fibrous capsule
- Frequently contain necrotic debris (anchovy paste)

MICROSCOPIC

Histologic Features

- Early lesion
  - Trophozoites within sinusoids
  - Focal necrosis
  - Neutrophilic infiltrate with edema
- Later lesion
  - Necrotic material
    - Abundant nuclear debris but few intact inflammatory cells
  - Organisms most often at advancing edge; may be hard to find
  - Mononuclear cells at advancing edge, along with edema
  - Eventually develop fibrosis and granulation tissue
- Morphologic features of organism
  - Foamy cytoplasm and distinct cell membrane
  - Eccentric round nucleus
    - Peripheral margination of chromatin, central karyosome
  - Ingested red blood cells essentially pathognomonic of *E. histolytica*
  - Trophozoites are PAS, trichrome (+)

DIFFERENTIAL DIAGNOSIS

Neoplasms

- May mimic amebic abscess radiographically

Pyogenic Liver Abscess

- Pyogenic abscess usually has more neutrophils, lacks parasites
- Aspiration with culture helps resolve

Macrophages

- Macrophages mark by immunohistochemistry (e.g., CD68)
- Amebic nuclei rounder, more open chromatin pattern than macrophages

Entamoeba dispar

- Morphologically identical but noninvasive

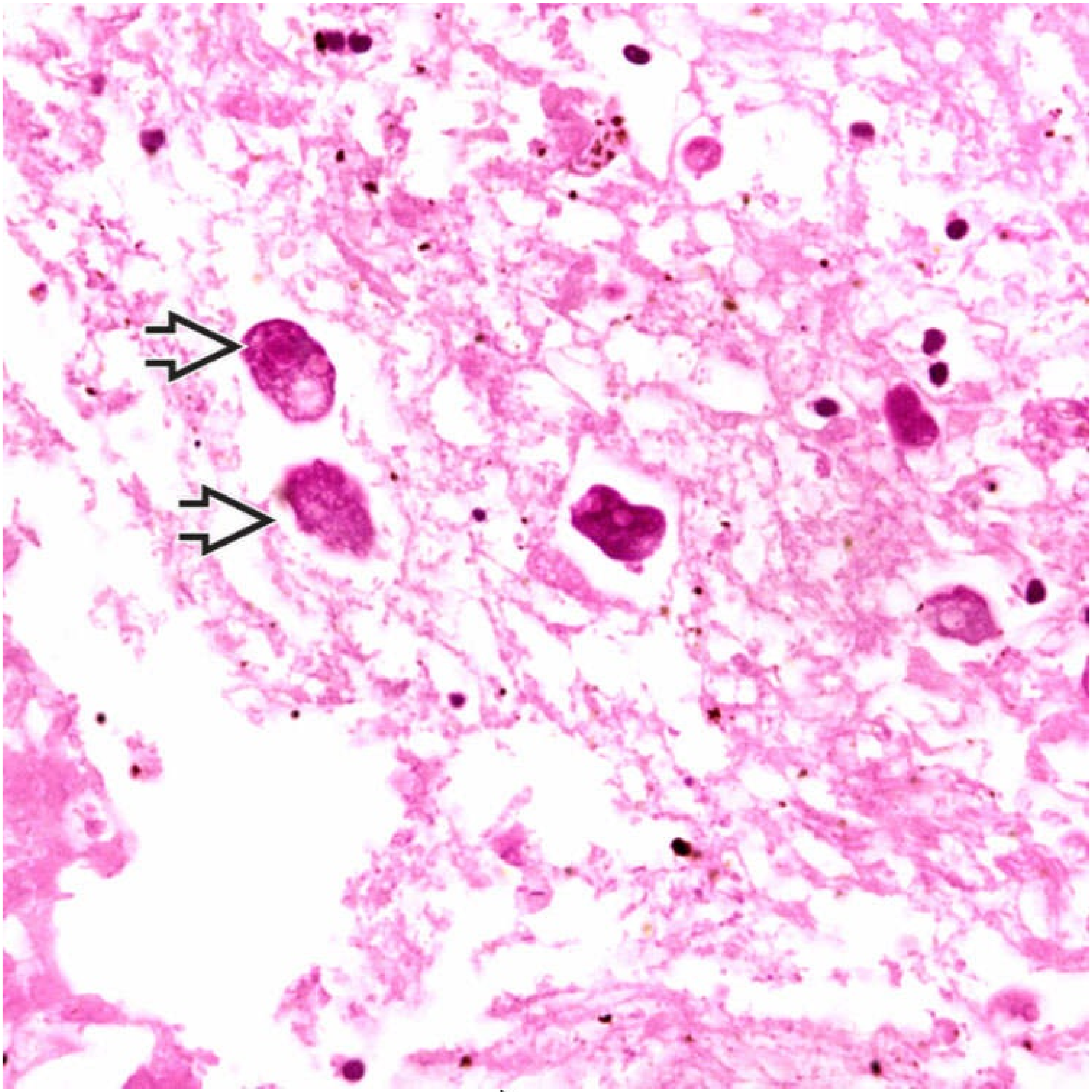
Balantidium coli

- Large ciliate with kidney bean-shaped nucleus

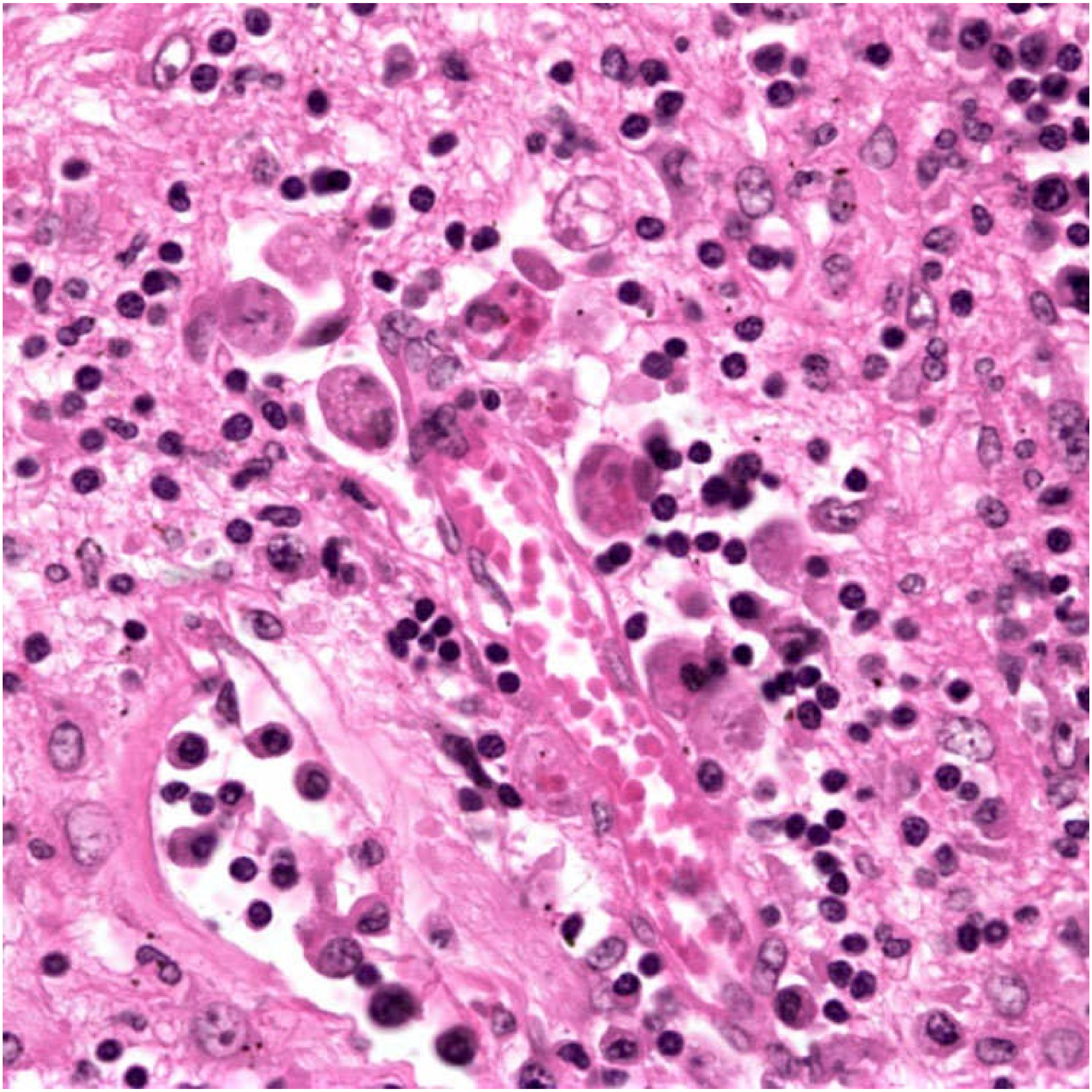
DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Look for protozoa in amorphous necrotic material with few intact inflammatory cells
- Ameba may closely resemble macrophages



Periodic acid-Schiff stain highlights amebae ➪ within amorphous necrotic debris. Note that there is nuclear debris present but no intact neutrophils.



Amebae are present with admixed mononuclear cells and necrotic debris.

SELECTED REFERENCES

1. Zebardast, N, et al. Application of multiplex PCR for detection and differentiation of Entamoeba histolytica, Entamoeba dispar and Entamoeba moshkovskii. *Iran J Parasitol*. 2014; 9(4):466–473.
2. Hung, CC, et al. Entamoeba histolytica infection in men who have sex with men. *Lancet Infect Dis*. 2012; 12(9):729–736.
3. Wuerz, T, et al. A review of amoebic liver abscess for clinicians in a nonendemic setting. *Can J Gastroenterol*. 2012; 26(10):729–733.
6. Maltz, G, et al. Amebic liver abscess: a 15-year experience. *Am J Gastroenterol*. 1991;

86(6):704–710.

4. Fotedar, R, et al. Laboratory diagnostic techniques for Entamoeba species. *Clin Microbiol Rev*. 2007; 20(3):511–532. [table of contents].
5. Sharma, MP, et al. Amoebic liver abscess. *Trop Gastroenterol*. 1993; 14(1):3–9.
7.Greenstein, AJ, et al. Pyogenic and amebic abscesses of the liver. *Semin Liver Dis*. 1988; 8(3):210–217.
8.Brandt, H, et al. Pathology of human amebiasis. *Hum Pathol*. 1970; 1(3):351–385.

Schistosomiasis

KEY FACTS

Terminology

- Parasitic infection caused by trematodes (blood flukes) of genus *Schistosoma*
  - *S. mansoni* and *S. japonicum* most frequently cause hepatosplenic disease

Etiology/Pathogenesis

- Infection occurs when cercariae (infectious larvae) leave intermediate host snail and penetrate skin of vertebrate host (in contaminated water)

Clinical Issues

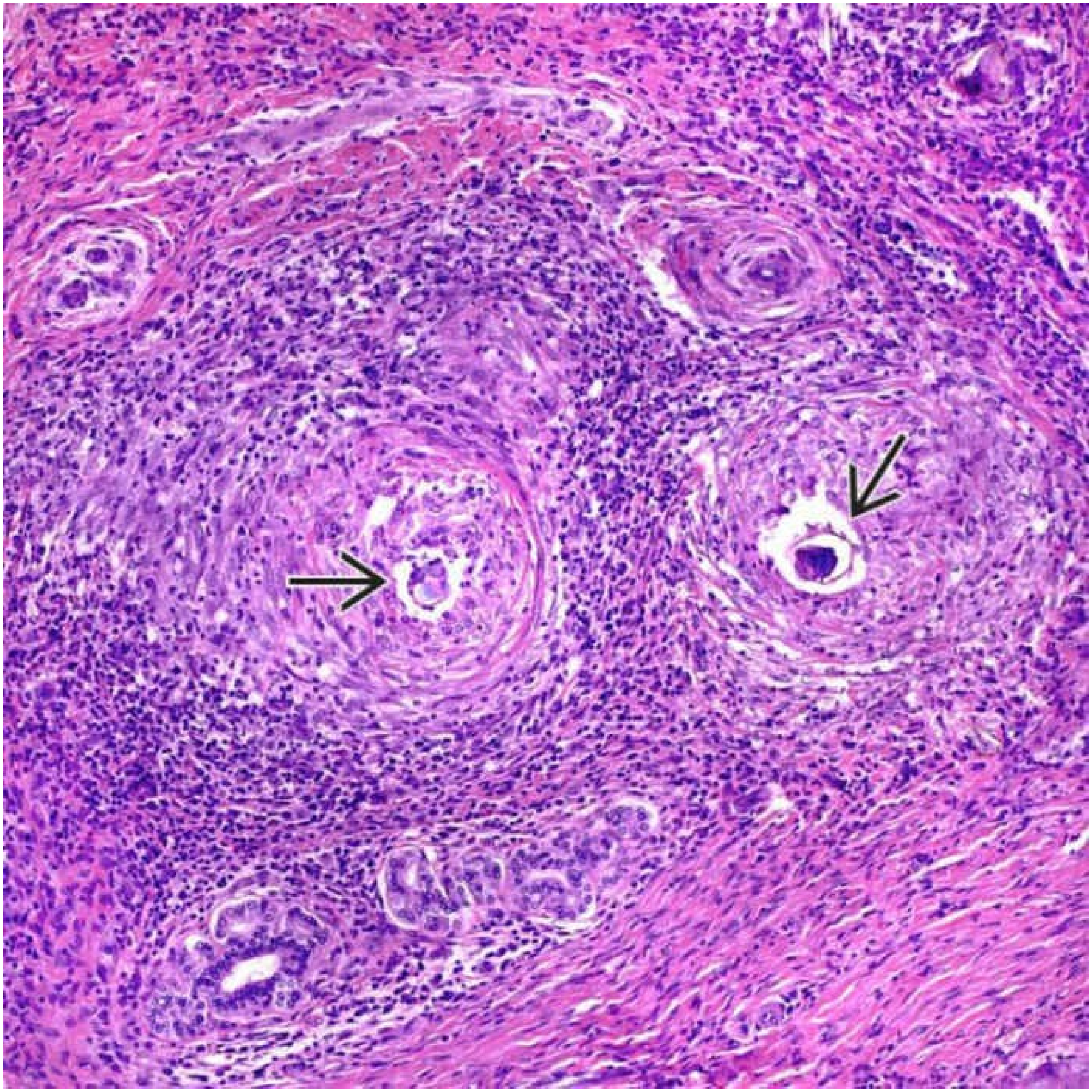
- Each *Schistosoma* species associated with specific snail species, which determines geographic distribution
  - 85% of infections are in sub-Saharan Africa
- Acute presentation (Katayama fever) is hypersensitivity reaction to schistosome antigens
- Chronic disease is secondary to tissue damage from inflammatory response to ova, not worms themselves
- 10% of patients progress to severe hepatic fibrosis
  - Hepatic function preserved until late in disease course
- Laboratory tests
  - Stool or urine examination for ova
  - Serology to detect antischistosomal antibodies

Microscopic

- Portal fibrosis with partial or complete destruction of main branches of portal vein and sparing of arteries and ducts
- Granulomatous reaction to ova with variably present foreign body giant cells, eosinophils, mononuclear cells
- Ova have refractile shell and lateral spine
- Hematin pigment in portal and sinusoidal macrophages

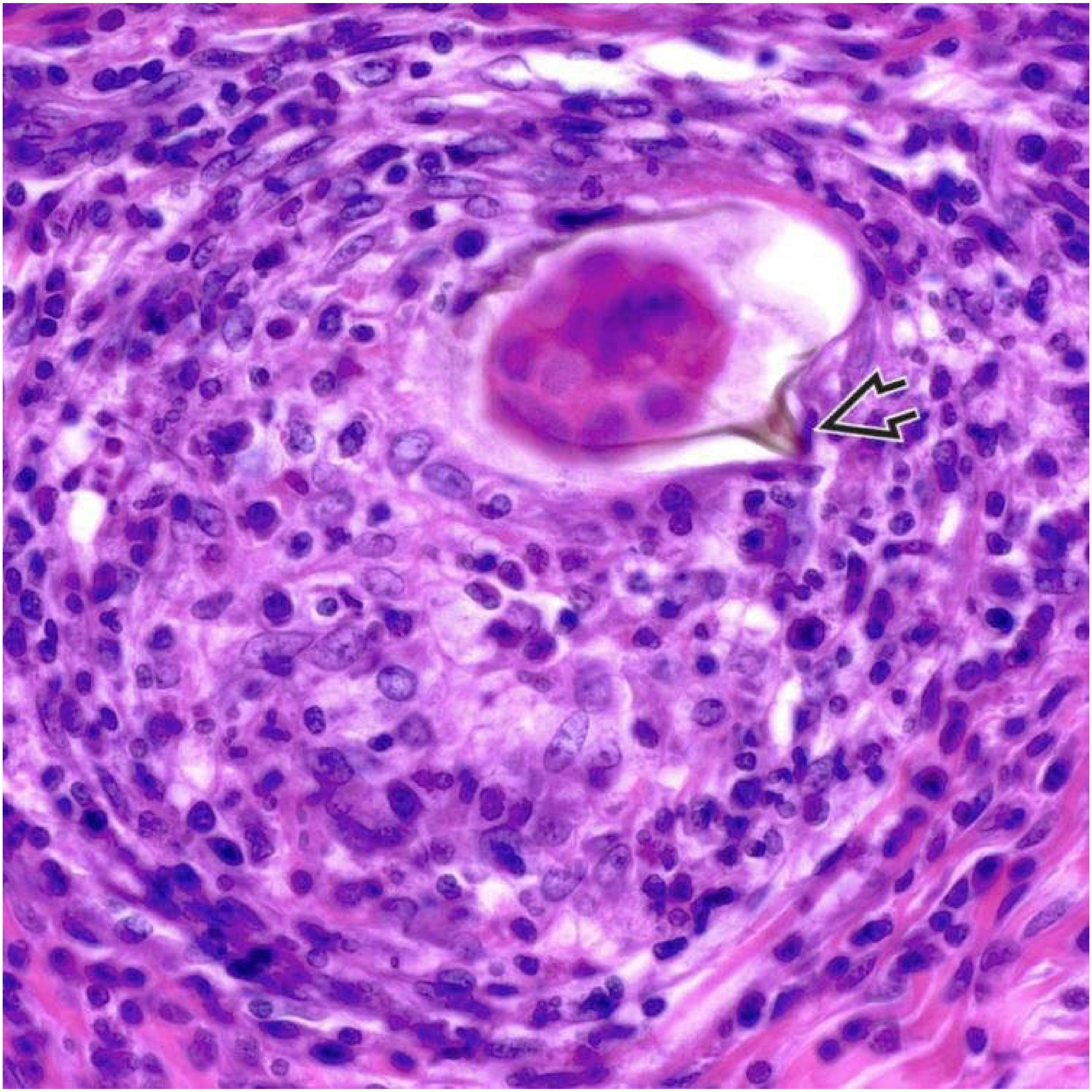
Diagnostic Checklist

- Granulomatous hepatitis in patient from endemic area warrants search for ova



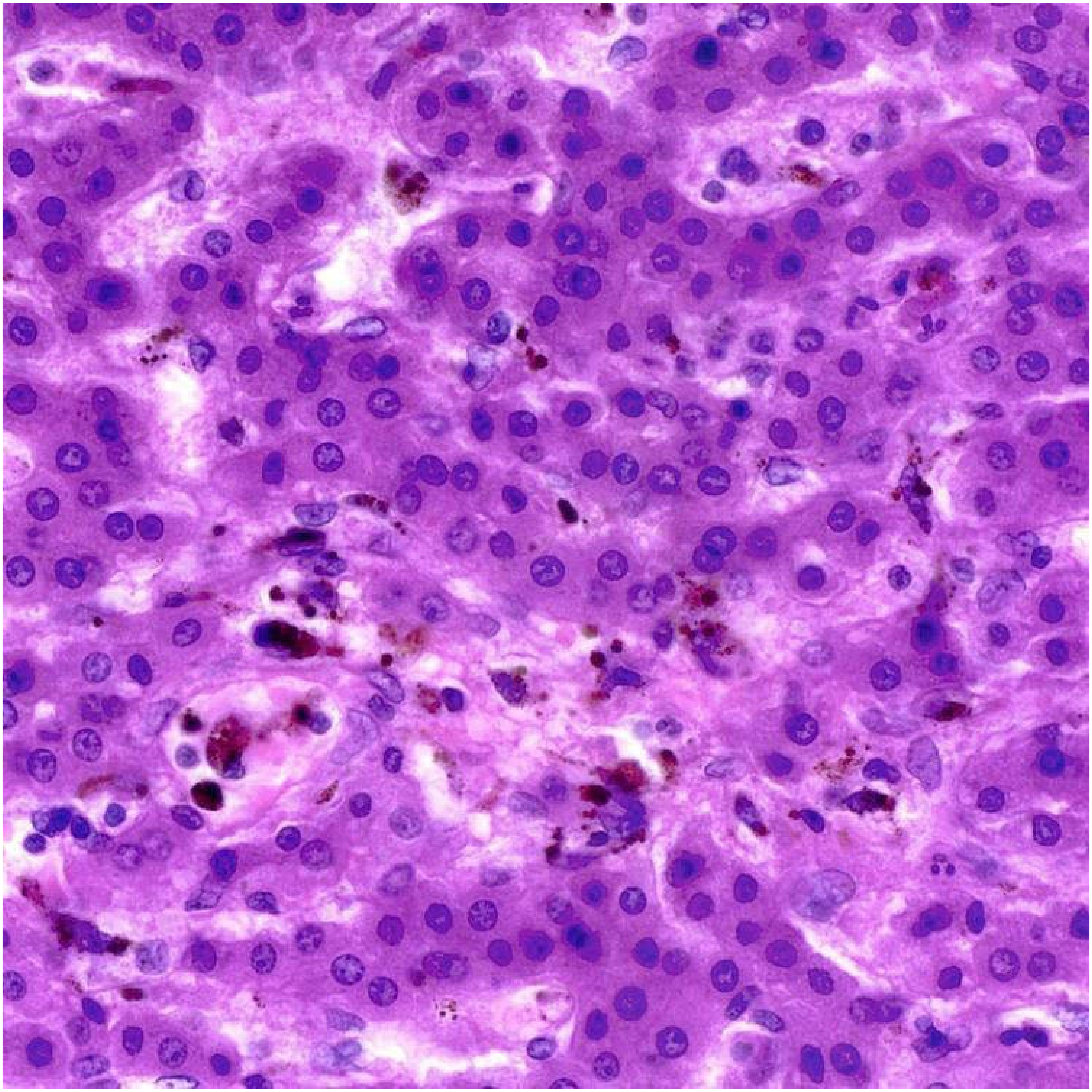
Ova and Granulomas

This expanded and markedly fibrotic portal area contains numerous granulomas with central ova →; some are clearly embryonated. There is associated chronic inflammation, but eosinophils are not prominent in this case.



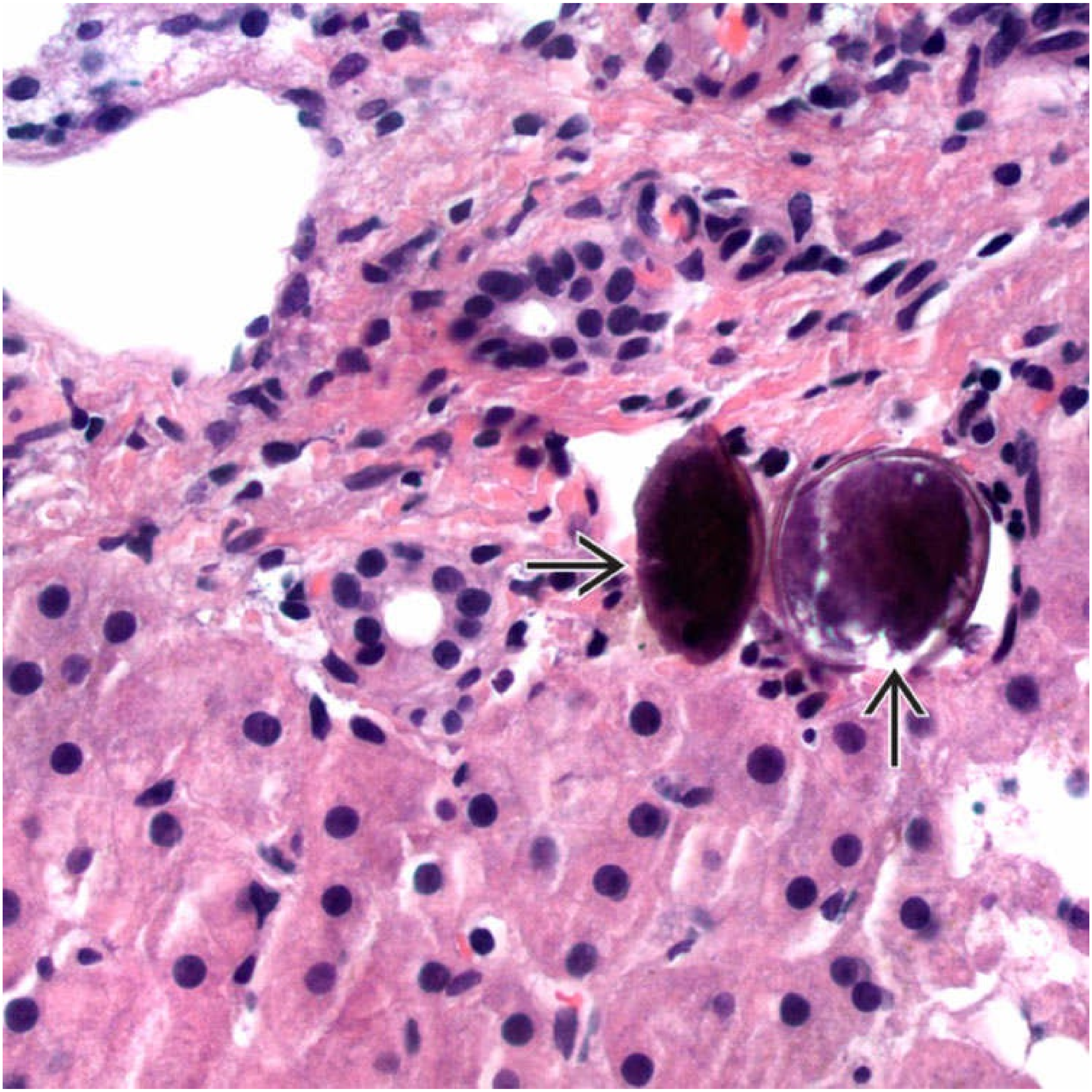
Embryonated Egg

This portal granuloma contains an embryonated egg with a lateral spine ⇨ .



Hematin Pigment

Macrophages in the portal tracts and sinusoids contain dark brown pigment, consistent with hematin, which is regurgitated by the flukes after metabolizing hemoglobin.



Calcified Eggs
Two calcified ova are present in a portal tract →, possibly in a small venule; the spines are not visible. In this case, a granulomatous reaction is not present. The lack of inflammation and calcification of the ova implies remote infection.

TERMINOLOGY

Synonyms

• Bilharziasis, snail fever, Katayama fever

Definitions

• Parasitic infection caused by trematodes (blood flukes) of genus *Schistosoma*

- 3 major species cause infection in humans: *S. mansoni*, *S. haematobium*, *S. japonicum*
  - *S. mansoni* and *S. japonicum* more likely to cause disease in liver and bowel

ETIOLOGY/PATHOGENESIS

Life Cycle and Infection

- Infected humans/animals contaminate fresh water with eggs by urine or feces
  - Eggs release miracidia, which penetrate snails
  - Infection occurs when cercariae (infectious larvae) exit snail and penetrate skin of vertebrate host (in contaminated water)
  - Cercaria transform into migrating schistosomulum and gain access to venous system
  - After maturing, travel to mesenteric venous plexus, where male occupies gynecophoric canal of female
  - Adult flukes live 3-5 years on average, during which they feed on host blood and release eggs
- Eggs released into environment through intestine or GU tract hatch into miracidia, which again infect freshwater snails

CLINICAL ISSUES

Epidemiology

- Age
  - Children are infected as soon as they begin to have contact with fresh water; prevalence peaks in older school-age children
- Geographic distribution
  - Each *Schistosoma* species associated with specific snail species, which determines geographic distribution
    - Tropical countries in Africa, Caribbean, eastern South America, Southeast Asia, Middle East
    - 85% of infections are in sub-Saharan Africa

Presentation

- Acute presentation (Katayama fever)
  - Hypersensitivity reaction to schistosome antigens
  - Abdominal pain, cough, diarrhea, eosinophilia, fever, hepatosplenomegaly, rash
- Chronic presentation
  - Due to cumulative deposition of eggs in tissue
    - Portal hypertension with esophageal varices, splenomegaly, and thrombocytopenia
      - Extrahepatic manifestations include colonic polyposis with bloody diarrhea, cystitis with hematuria, and pulmonary hypertension
    - Tissue damage is related to inflammatory response to ova trapped in host tissue, not worms themselves
    - Schistosomiasis potentiates HBV and HCV infection in liver

Laboratory Tests

- Stool or urine examination for ova

- May require multiple specimens, as shedding of eggs varies widely
- Serology to detect antischistosomal antibodies
  - Several commercially available techniques; sensitivity/specificity depend on technique used
  - Serologies do not distinguish between prior and current infection

Treatment

- Drugs
  - Praziquantel

Prognosis

- 10% of patients progress to severe hepatic fibrosis
  - Liver function typically preserved until late-stage disease

MICROSCOPIC

Portal Fibrosis and Inflammation

- Partial or complete destruction of main branches of portal vein
  - Inflammation induced by eggs leads to pyelophlebitis, periportal fibrosis
  - "Symmers pipe stem fibrosis" characterized by marked portal fibrosis but preserved lobular architecture
- Arteries and ducts are spared

Granulomatous Reaction to Ova

- Variably present foreign body giant cells, eosinophils, mononuclear cells
- Ova have refractile shell and lateral spine (*S. mansoni* and *S. japonicum*)
- Sometimes only degenerated parts of eggs are present
- Remote infections often feature calcified eggs without active inflammation

Pigment

- In sinusoids and portal tracts; caused by adult worms metabolizing hemoglobin and regurgitating hematin pigment

DIFFERENTIAL DIAGNOSIS

Sarcoidosis

- Numerous granulomas without ova; eosinophils not feature

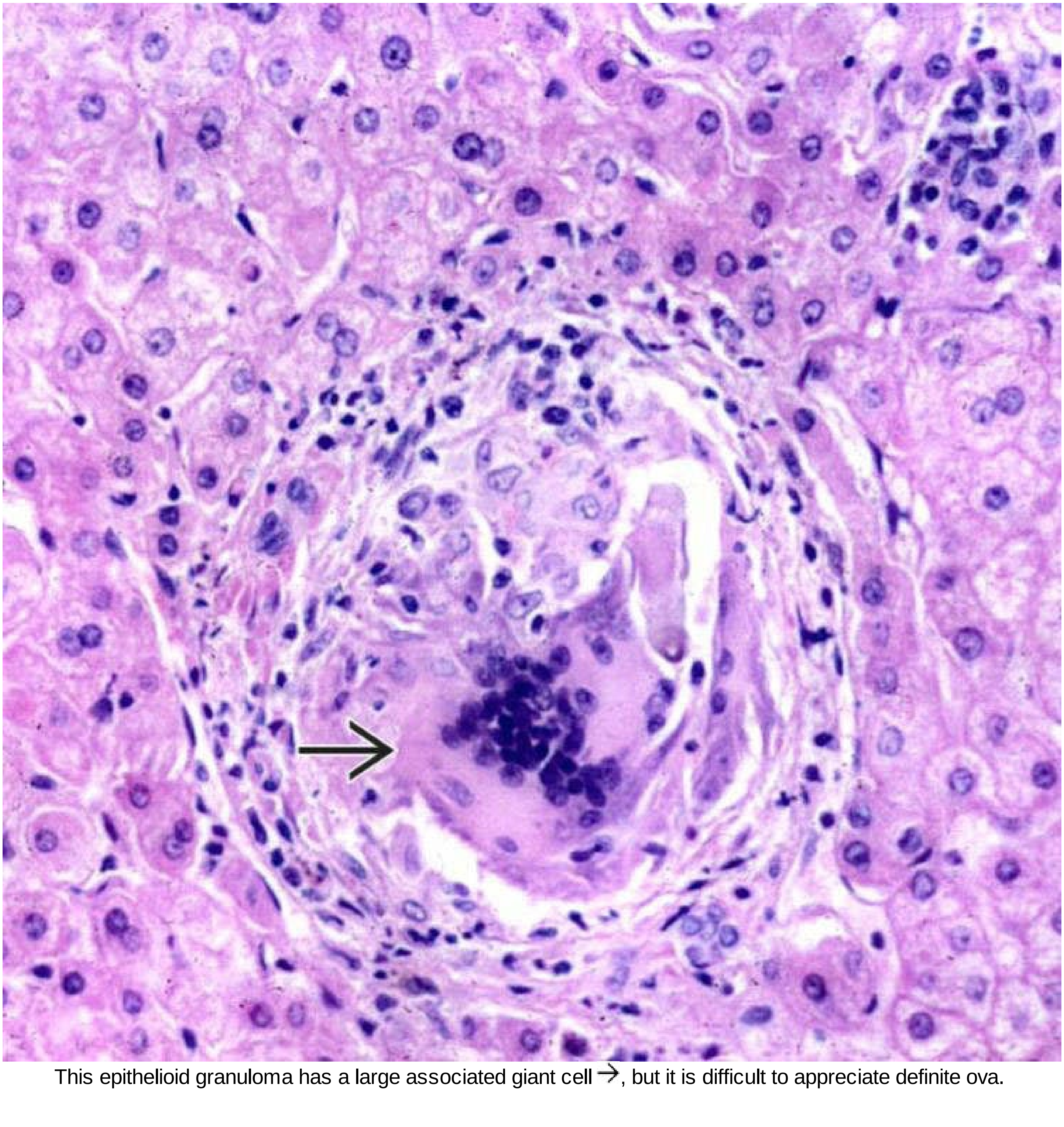
Other Parasitic &/or Granulomatous Infections

- *Ascaris*, *Enterobius*, fungal infections, tuberculosis; schistosome eggs help to distinguish

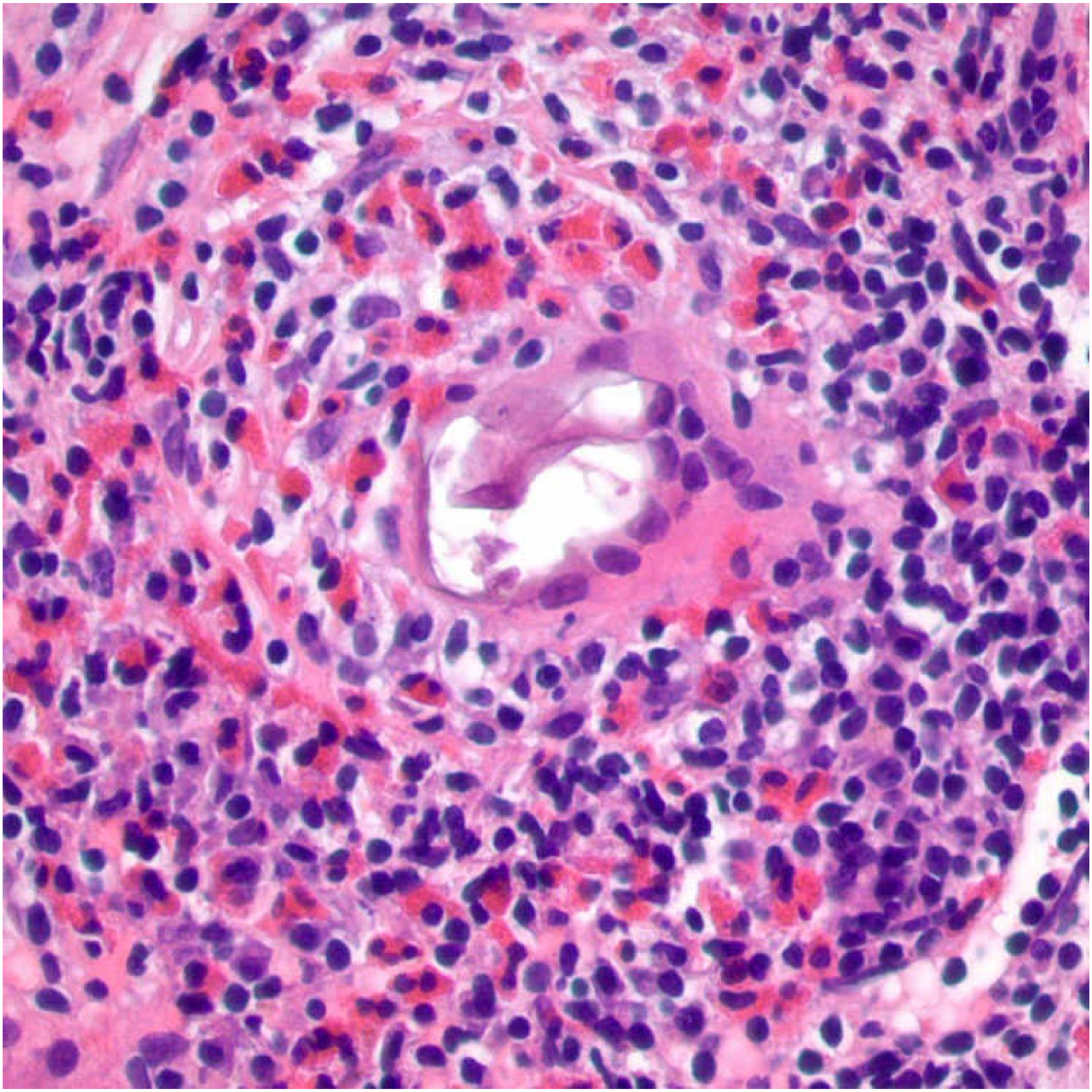
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

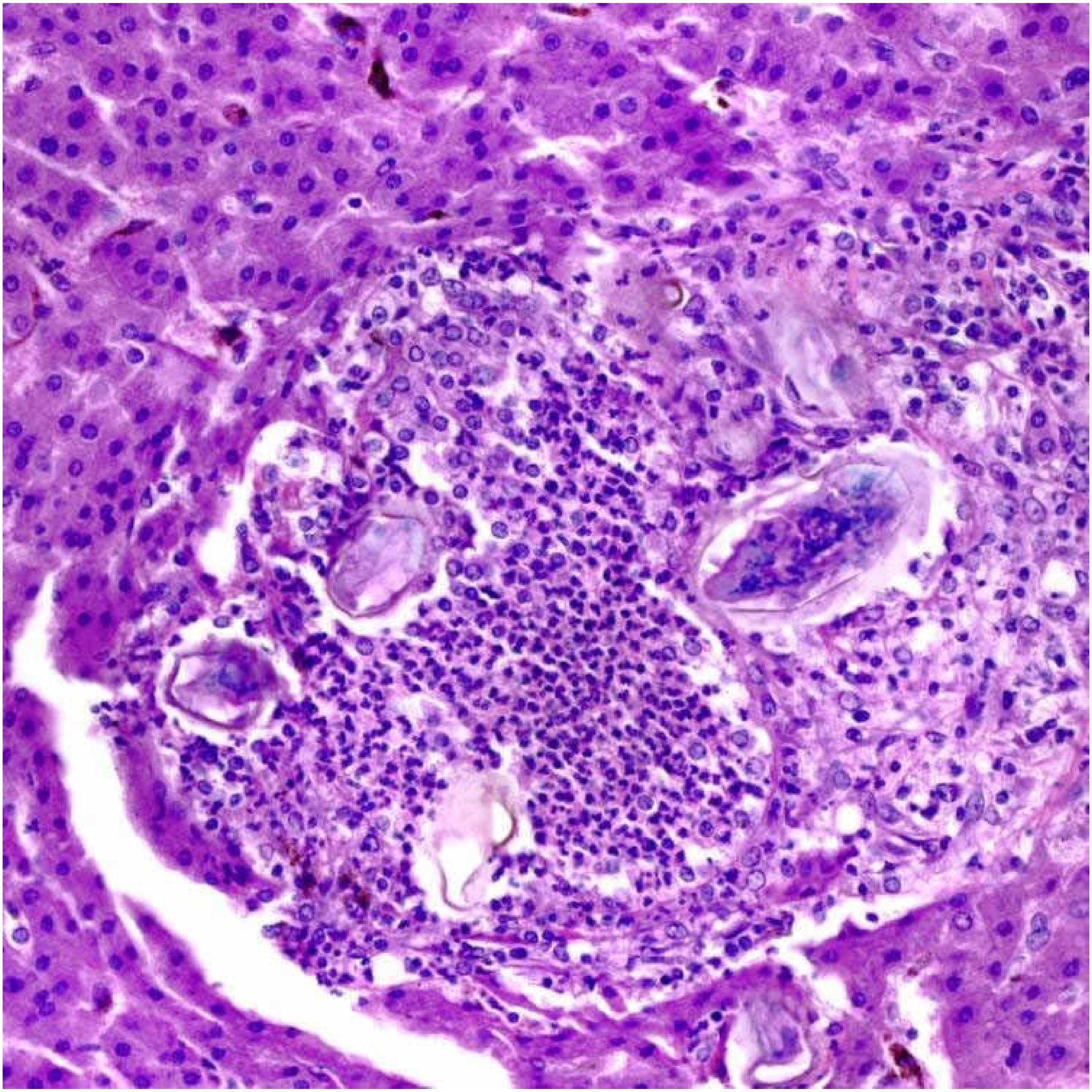
- Granulomatous hepatitis in patient from endemic area warrants search for ova
  - Important cause of presinusoidal portal hypertension in patients from endemic areas
  - Liver function is maintained, so patients lack stigmata of liver insufficiency



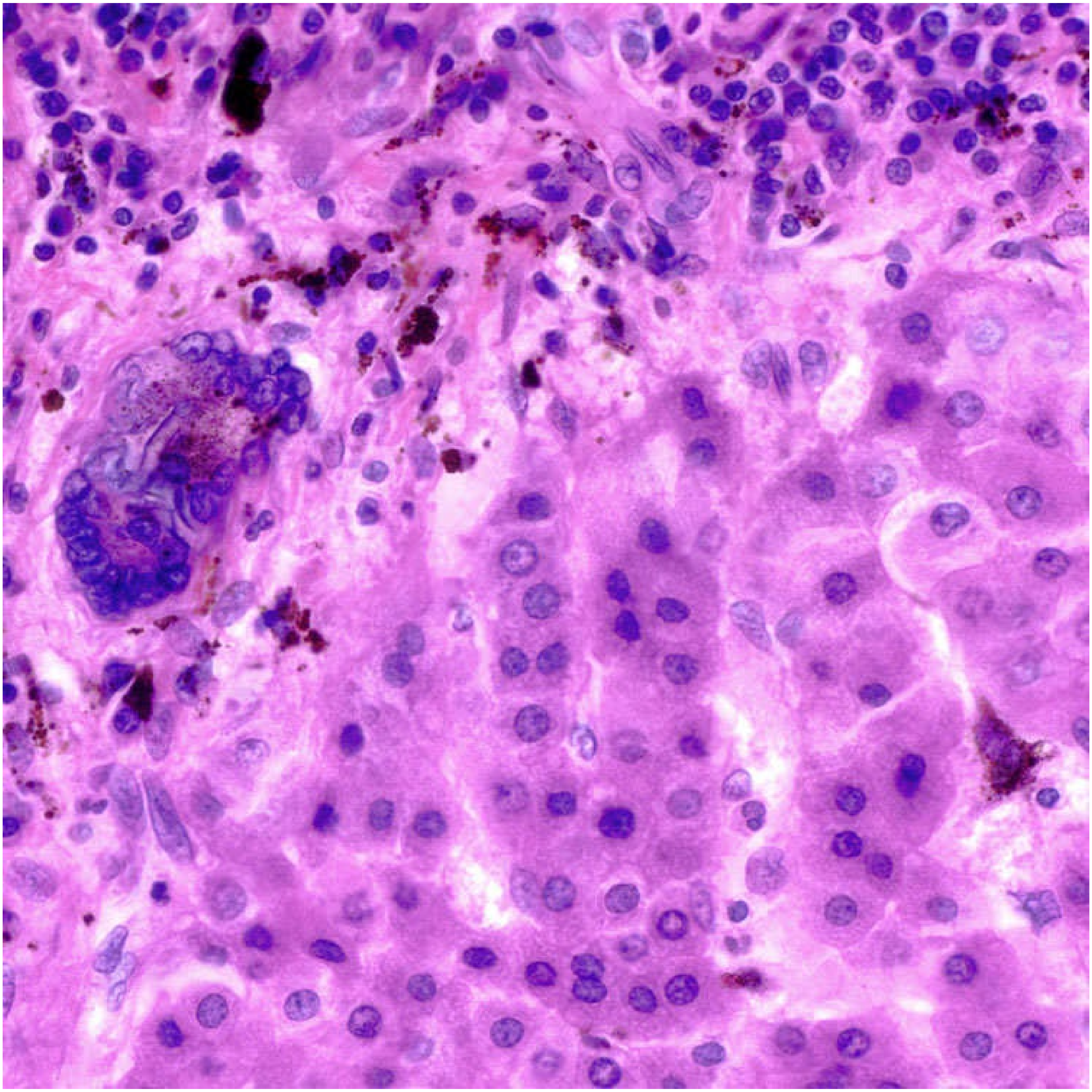
This epithelioid granuloma has a large associated giant cell →, but it is difficult to appreciate definite ova.

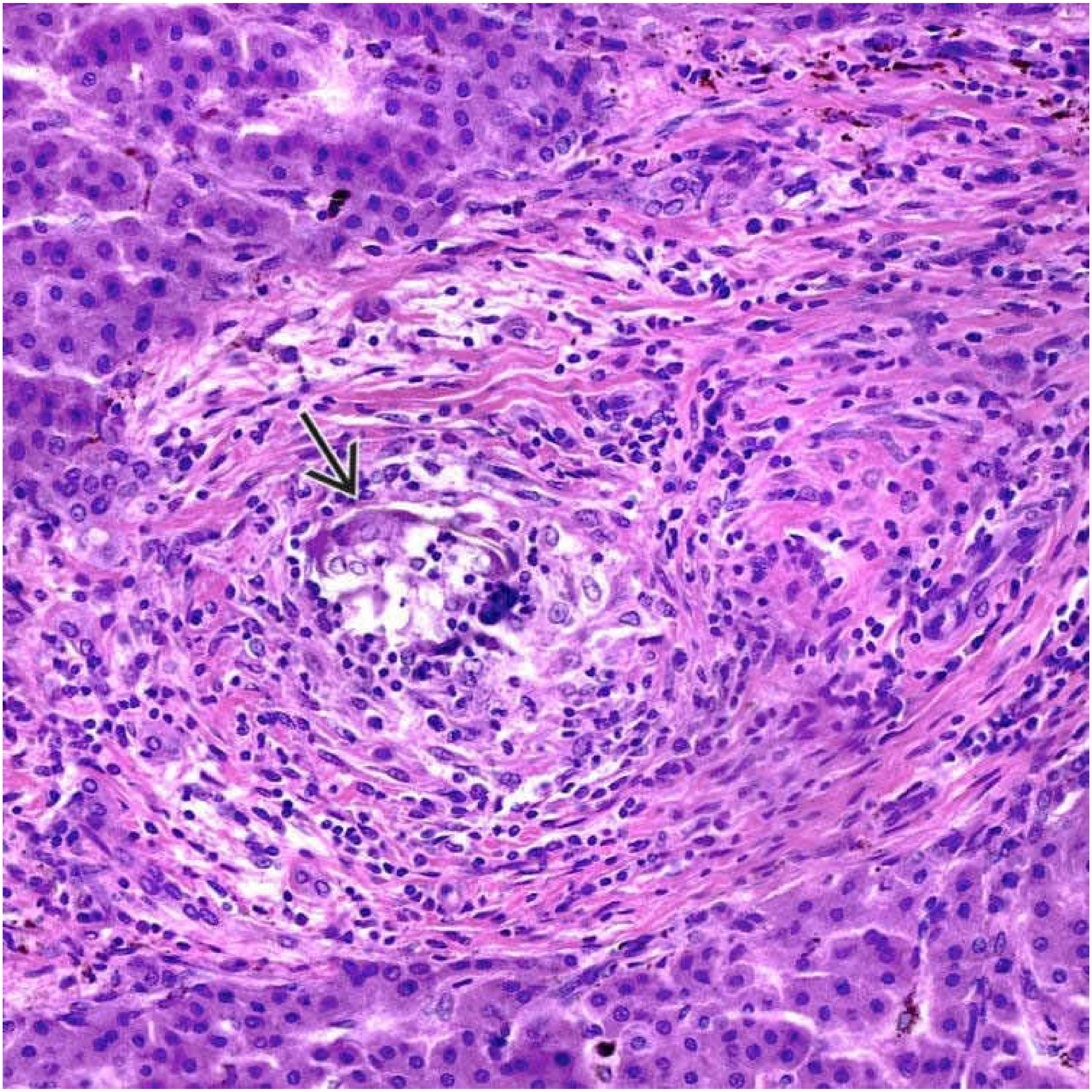


A giant cell engulfing degenerate egg fragments is surrounded by numerous eosinophils and mononuclear cells.

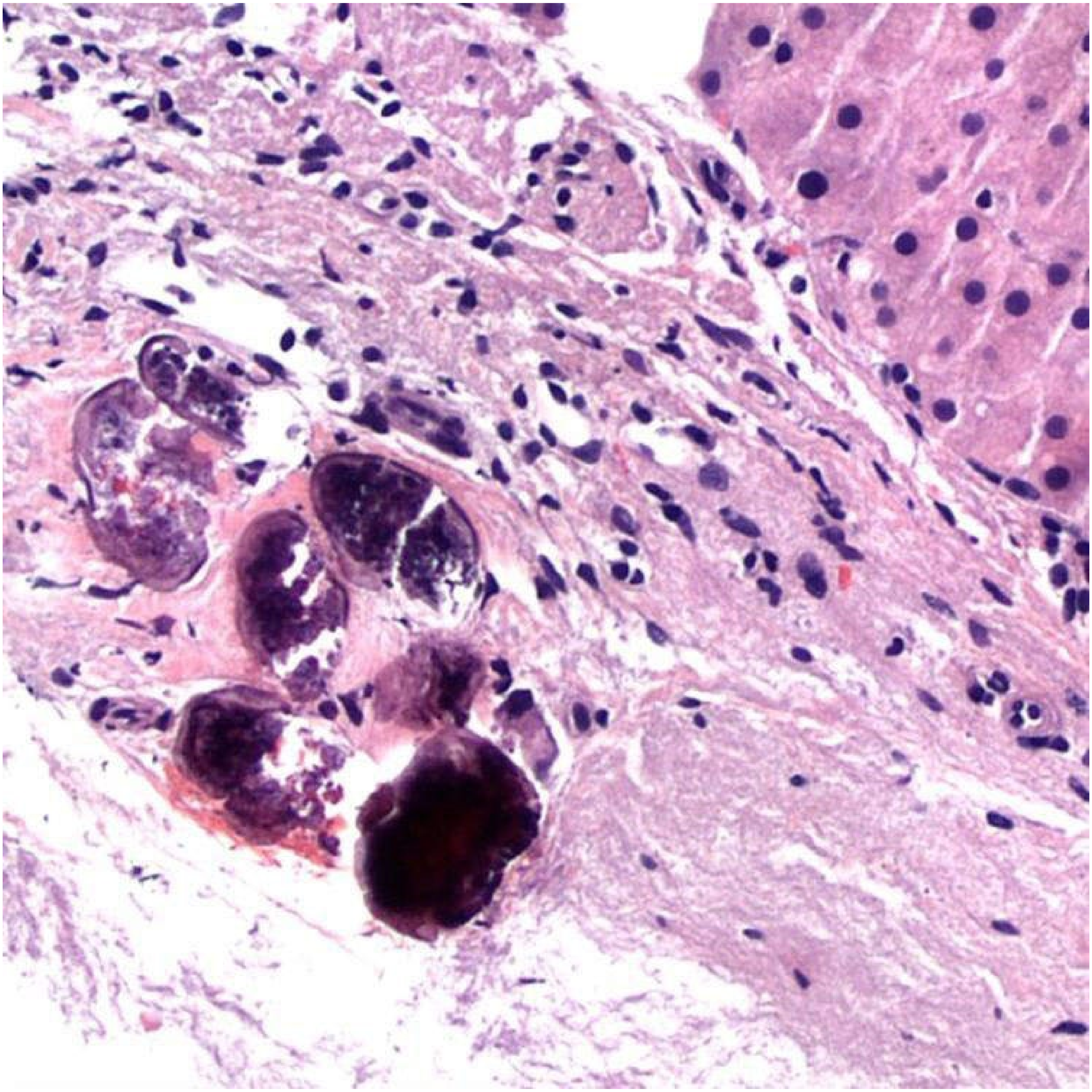


This granuloma contains multiple intact embryonated eggs, and has associated eosinophils and neutrophils. Note the hematin pigment in the adjacent parenchyma.

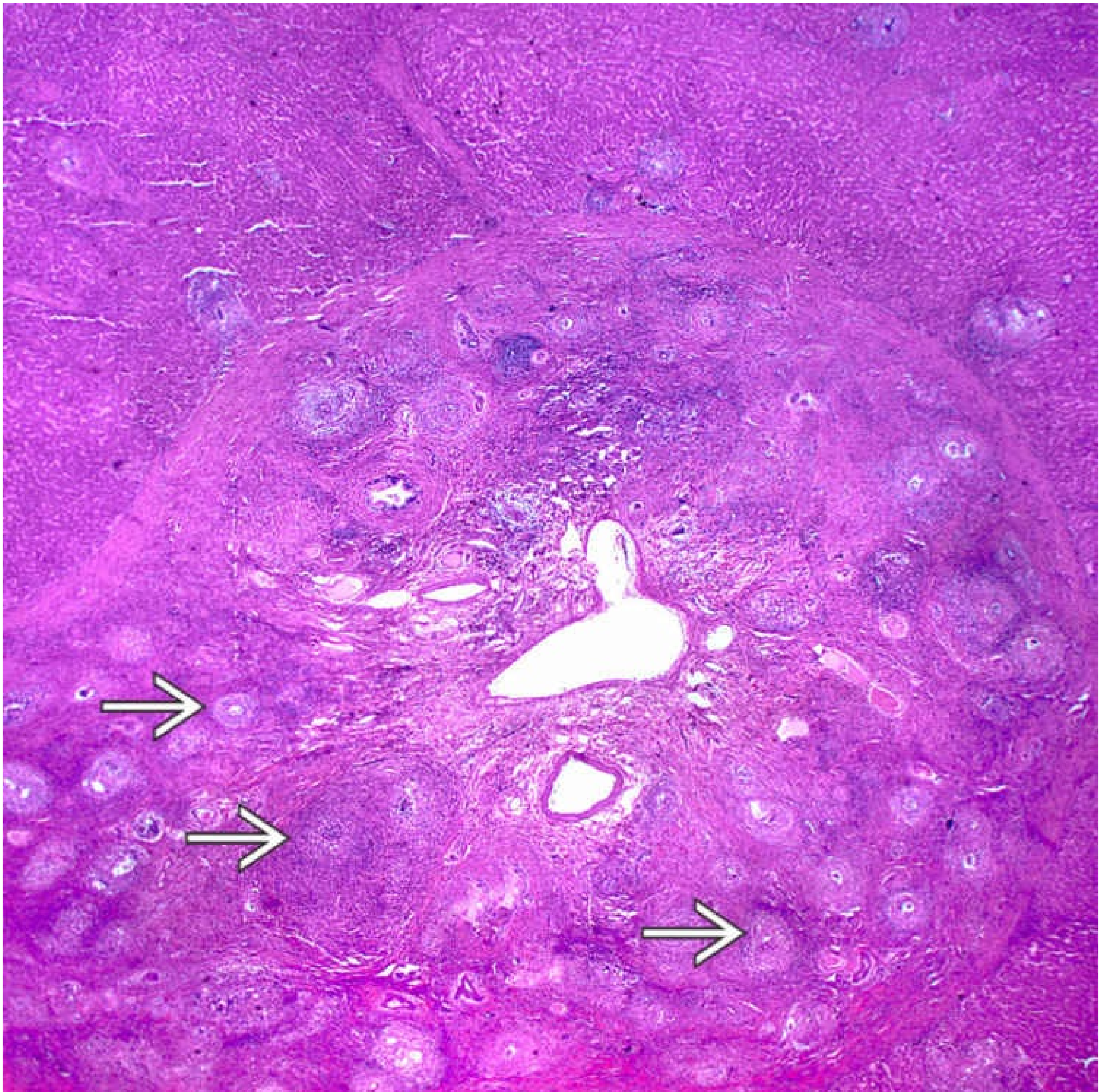

Hematin pigment is present within both portal and sinusoidal macrophages.



This portal tract is fibrotic, and contains a granuloma with associated chronic inflammation and degenerated eggs →. Note the hematin pigment within macrophages.



This portal tract contains several calcified ova, but no inflammation, suggesting remote infection.



A markedly enlarged portal tract contains numerous rounded nodules ⇨ that consist of ova with surrounding granulomatous reaction. The enlarged portal area has no associated fibrotic septa.

SELECTED REFERENCES

1. Shaker, Y, et al. Hepatobiliary schistosomiasis. *J Clin Transl Hepatol*. 2014; 2(3):212–216.
2. Elbaz, T, et al. Hepatic and intestinal schistosomiasis: review. *J Adv Res*. 2013; 4(5):445–452.
3. Gryseels, B, et al. Human schistosomiasis. *Lancet*. 2006; 368(9541):1106–1118.
4. Kibiki, GS, et al. Hepatosplenic schistosomiasis: a review. *East Afr Med J*. 2004; 81(9):480–485.
5. Vennervald, BJ, et al. Morbidity in schistosomiasis: an update. *Curr Opin Infect Dis*. 2004; 17(5):439–447.
6. Bica, I, et al. Hepatic schistosomiasis. *Infect Dis Clin North Am*. 2000; 14(3):583–604. [viii].

7. Elliott, DE. Schistosomiasis. Pathophysiology, diagnosis, and treatment. *Gastroenterol Clin North Am*. 1996; 25(3):599–625.
8. Da Silva, LC, et al. Hepatosplenic schistosomiasis. Pathophysiology and treatment. *Gastroenterol Clin North Am*. 1992; 21(1):163–177.

Echinococcosis

KEY FACTS

Terminology

- Zoonotic infection caused by *Echinococcus* species
    - Cestode (tapeworm) with wide geographic distribution
- *E. granulosus* (cystic form) and *E. multilocularis* (alveolar form) most commonly infect humans

Etiology/Pathogenesis

- Humans infected by exposure to contaminated feces of primary or intermediate host

Clinical Issues

- Right lobe of liver is most common site
    - Often asymptomatic, given slow-growing nature of cysts (1 mm/month)
    - Symptoms usually due to space-occupying compression of other structures, or rupture
    - Bile duct obstruction, infection, portal hypertension
- Puncture with radiologic guidance, aspiration, infusion of protoscolicidal agent, reaspiration (PAIR) is preferred treatment
    - Patients with ruptured cystic disease may require lifelong antiparasitic therapy to prevent recurrence

Macroscopic

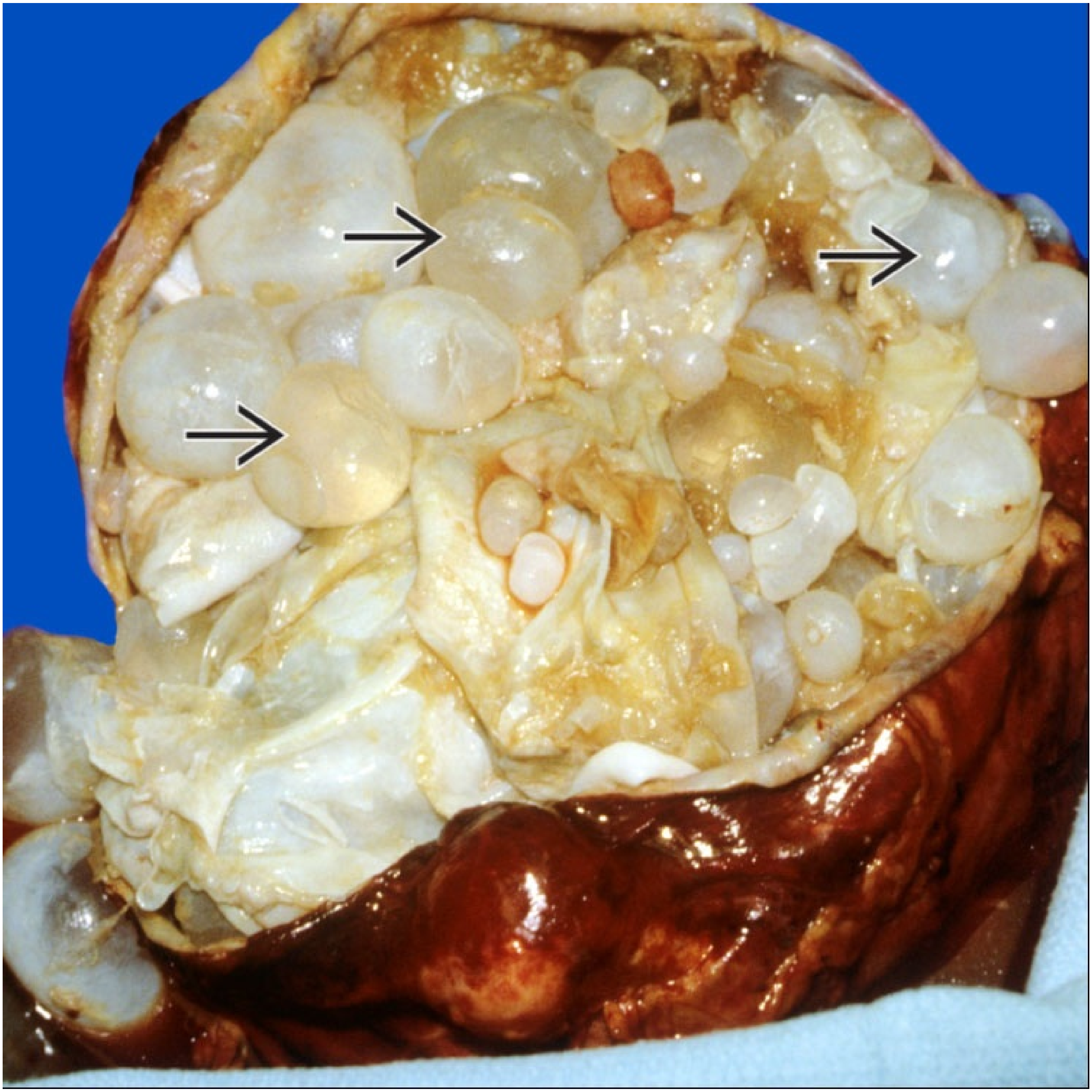
- *E. granulosus* produces unilocular cysts with fibrous rim, filled with milky material and smaller daughter cysts
- *E. multilocularis* is more likely to present as inflammatory or fibrotic masses with scattered cystic spaces

Microscopic

- Viable cysts of *E. granulosus* are composed of 3 layers
    - Innermost germinal membrane with protoscolices
    - Middle hyalinized, laminated, acellular material

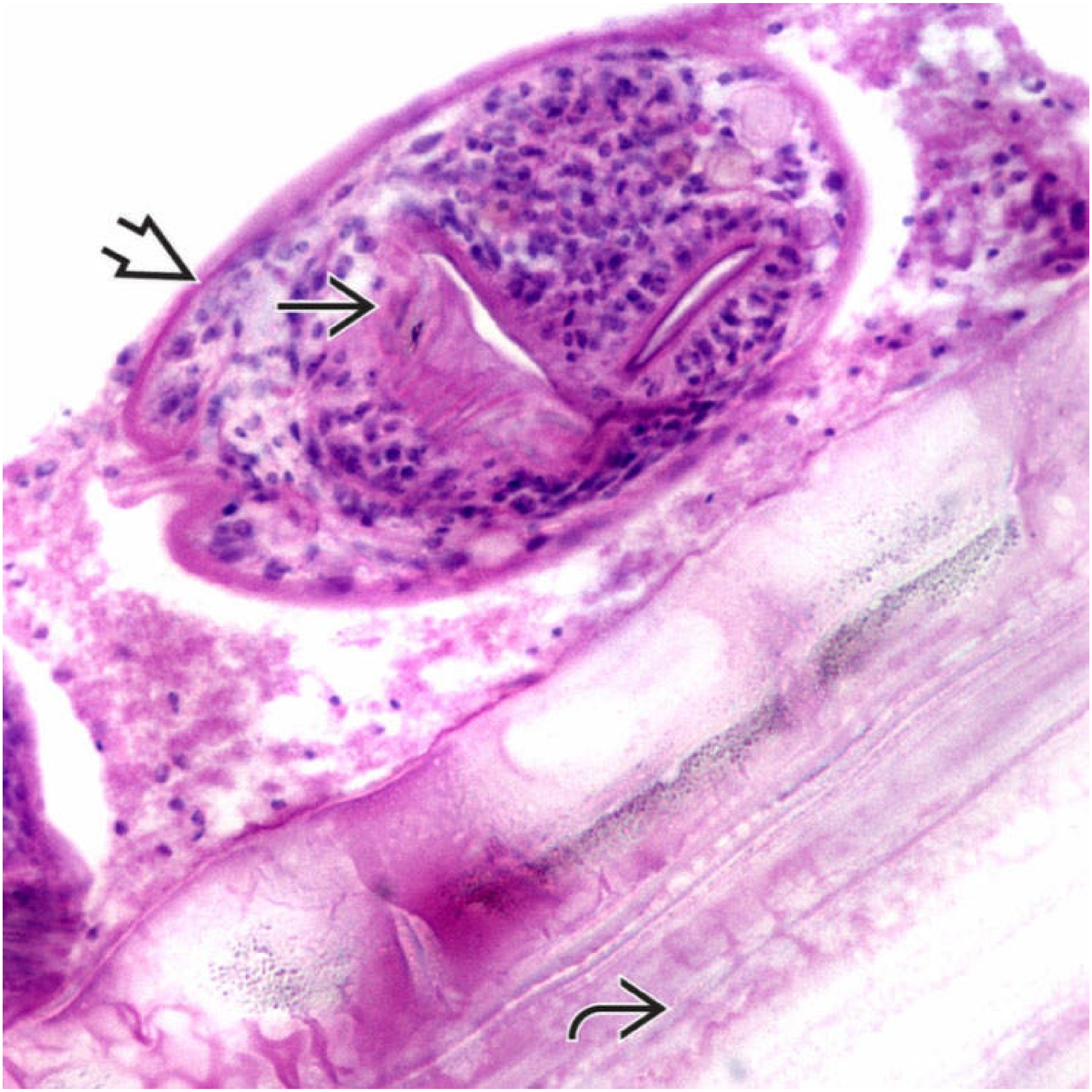
- Outer granulation tissue and fibrosis
- Daughter cysts are structurally identical to primary cyst

• *E. multilocularis* causes fibrotic mass with variably present daughter cysts and necrosis



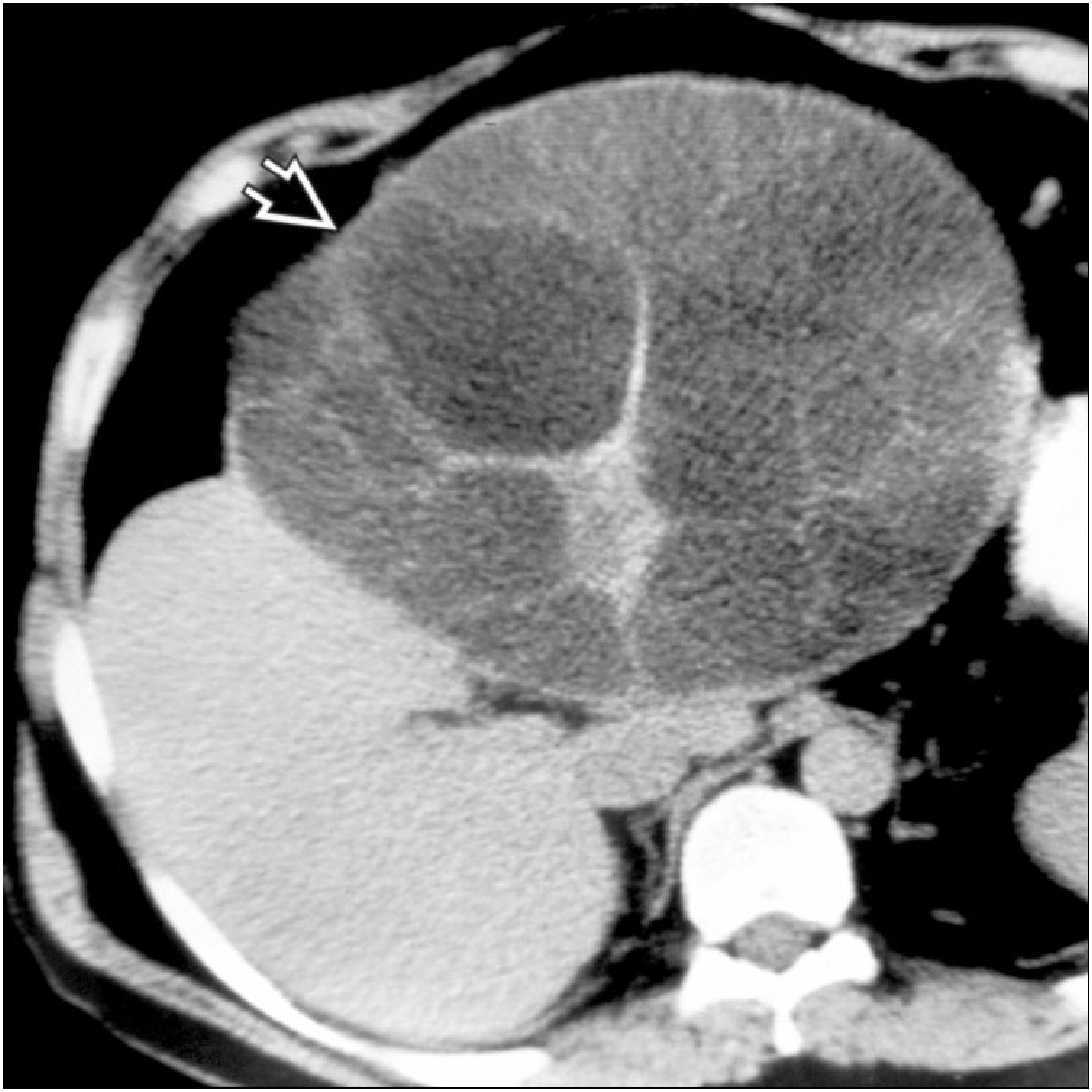
Gross Intraoperative Photograph

This intraoperative photograph of the liver shows a large hydatid cyst due to Echinococcus granulosus, containing multiple daughter cysts →, with a surrounding fibrous rim.

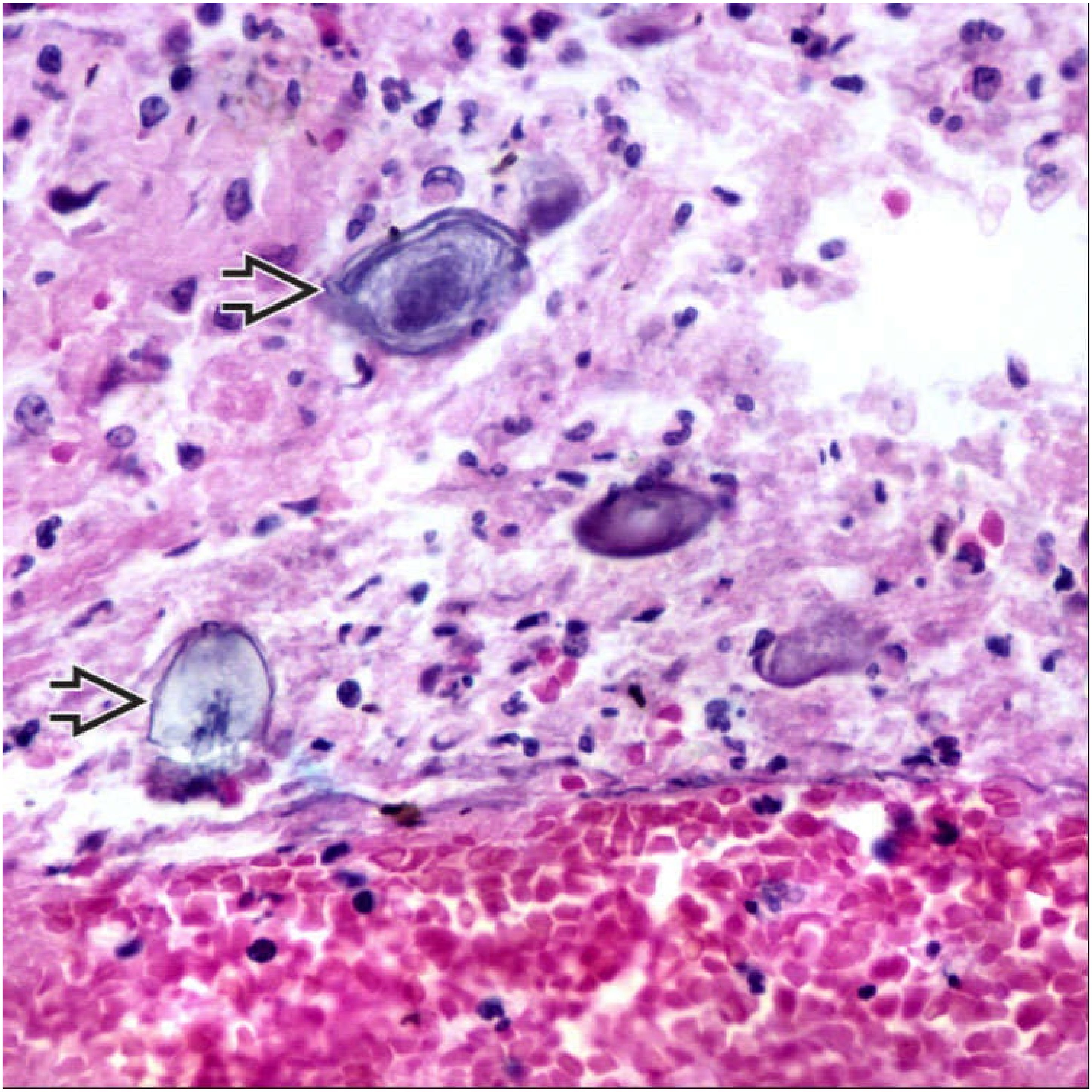


Cyst Lining

The inner lining of the echinococcal cyst gives rise to the brood capsule ➪ containing the developing scolices →. The next layer is composed of acellular, hyalinized material ↱.



Radiographic Image
This CT scan shows a very large hydatid cyst within the liver with internal septations ⇨ .



Degenerative Changes
Many echinococcal cysts are partially or completely degenerated upon resection and may contain only abundant debris with fragments of degenerated protoscolices ➪ .

TERMINOLOGY

Synonyms

• Hydatid disease

Definitions

• Zoonotic infection caused by *Echinococcus* species

- Cestode (tapeworm) with wide geographic distribution

- *Echinococcus granulosus* (cystic form) and *Echinococcus multilocularis* (alveolar form) most commonly infect humans

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Tapeworm attaches to small intestinal mucosa in definitive hosts (dogs or other carnivorous predator)
  - Humans infected by exposure to contaminated feces
  - After ingestion, eggs hatch, larval oncospheres pass to liver by portal vein
  - Cysts grow slowly (~ 1 mm per month)

CLINICAL ISSUES

Site

- Right lobe of liver is most common site
- May involve any site in body

Presentation

- Often asymptomatic, given slow-growing nature of cysts
  - Symptoms usually due to space-occupying compression of other structures or rupture
  - Bile duct compression, bacterial infection, cholangitis, rupture into peritoneal or pleural cavities
  - Rarely portal vein compression causes portal hypertension

Laboratory Tests

- Serologic studies
  - Cross reactivity with other cestodes
  - Intact (unruptured) cysts may not elicit antibody response

Treatment

- Complete surgical resection of cysts(s)
  - If ruptured, cyst fluid is highly antigenic, and leakage can result in urticaria or anaphylaxis as well as recurrence of infection
- Puncture, aspiration, injection, reaspiration (PAIR)
  - Puncture with radiologic guidance, aspiration, infusion of protoscolicidal agent, reaspiration
  - Preferred method as it decreases risk of anaphylaxis and recurrence

Prognosis

- Ruptured cystic disease may require lifelong antiparasitic therapy to prevent recurrence

IMAGING

General Features

- Ultrasound, CT scan show cysts with internal septations

MACROSCOPIC

General Features

- *E. granulosus*
  - Usually unilocular, filled with milky material and smaller daughter cysts
  - Fibrous rim; measure up to 35 cm
- *E. multilocularis* lesions are more likely to present as inflammatory or fibrotic masses with scattered cystic spaces

MICROSCOPIC

Histologic Features

- Viable cysts of *E. granulosus* have 3 layers
  - Innermost layer: Delicate germinal membrane
    - Thin lining of nucleated cells from which brood capsules and their enclosed protoscolices develop
    - Ovoid protoscolices represent incipient heads of adult tapeworms; contain 2 circles of hooklets and sucker
  - Middle layer: Hyalinized, white membrane of laminated, acellular material secreted by parasite
  - Outer peripheral layer: Granulation tissue and fibrosis
- Larger lesions may have daughter cysts that are structurally identical to primary cyst
  - Produced by protoscolices released from germinal membrane, or ruptured brood capsules
- Ruptured cysts may contain only fibroinflammatory debris with shed hooklets and calcification
- Eosinophils are not conspicuous unless cyst has degenerated or ruptured
- *E. multilocularis* causes fibrotic mass with variably present daughter cysts and necrosis
- Hooklets are partially acid-fast with Ziehl-Neelsen stain, stain with GMS, and are birefringent
- Polarization may also highlight hooklets

Cytologic Features

- Fine-needle aspiration fluid can be spun down and searched for protoscolices or hooklets

DIFFERENTIAL DIAGNOSIS

Other Tapeworm Infections

- Cysticercosis (*Taenia solium*); coenurosis (several species of tapeworm)

Fibropolycystic Liver Disease

- Lack tri-layered cyst, protoscolices

Amoebic or Pyogenic Abscess

- Lack tri-layered cyst, protoscolices

SELECTED REFERENCES

1. Manzano-Román, R, et al. Serological Diagnosis and Follow-Up of Human Cystic Echinococcosis: A New Hope for the Future? *Biomed Res Int*. 2015; 2015:428205.
2. Cappello, E, et al. Epidemiology and clinical features of cystic hydatidosis in Western Sicily: a ten-year review. *World J Gastroenterol*. 2013; 19(48):9351–9358.
3. Nunnari, G, et al. Hepatic echinococcosis: clinical and therapeutic aspects. *World J Gastroenterol*. 2012; 18(13):1448–1458.
4. Chrieki, M. Echinococcosis–an emerging parasite in the immigrant population. *Am Fam Physician*. 2002; 66(5):817–820.

SECTION 3
CHRONIC CHOLESTATIC AND AUTOIMMUNE DISORDERS

OUTLINE

Autoimmune Hepatitis

KEY FACTS

Terminology

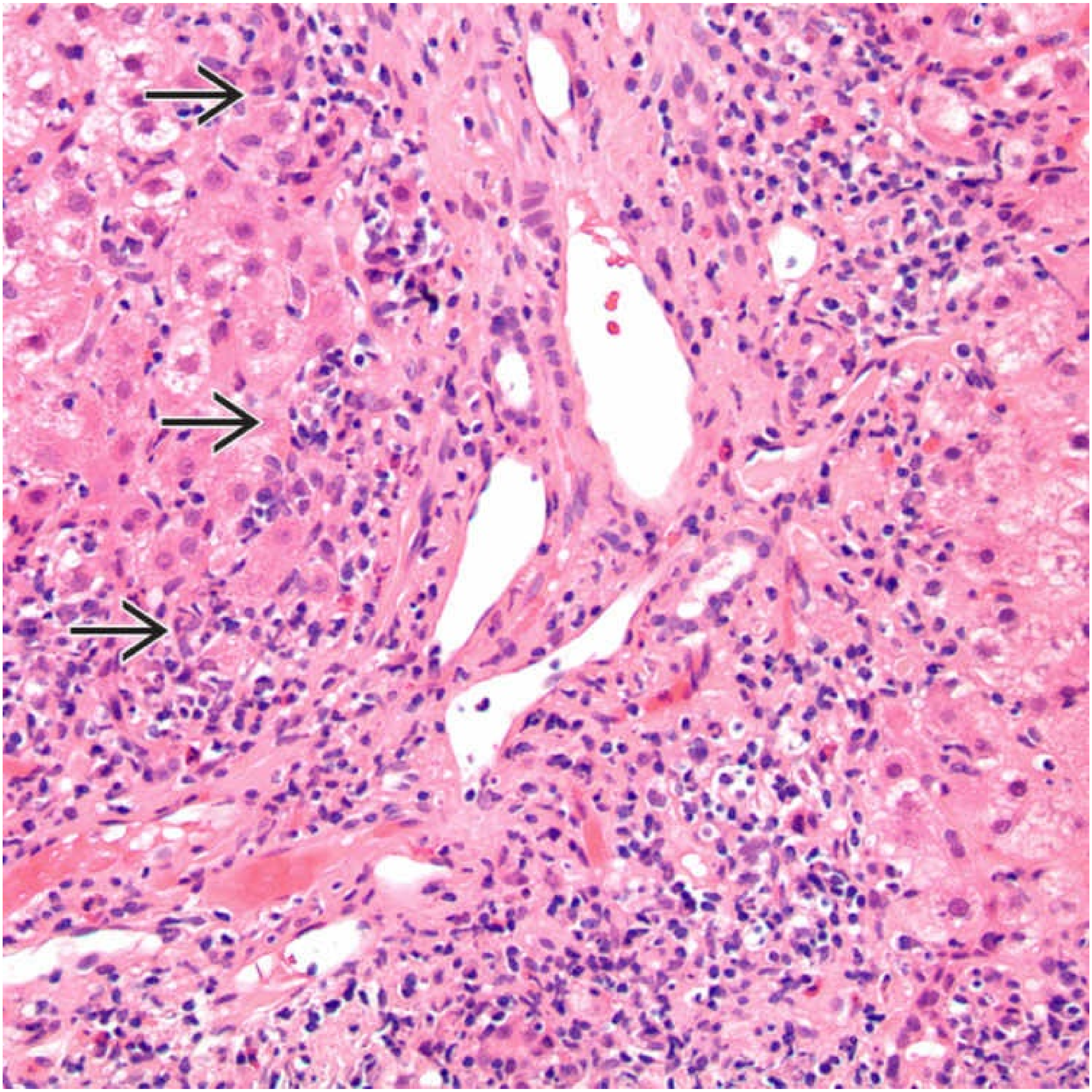
- Ongoing hepatitis, presumed autoimmune etiology
  - 3 types, based on identification of serum autoantibodies

Clinical Issues

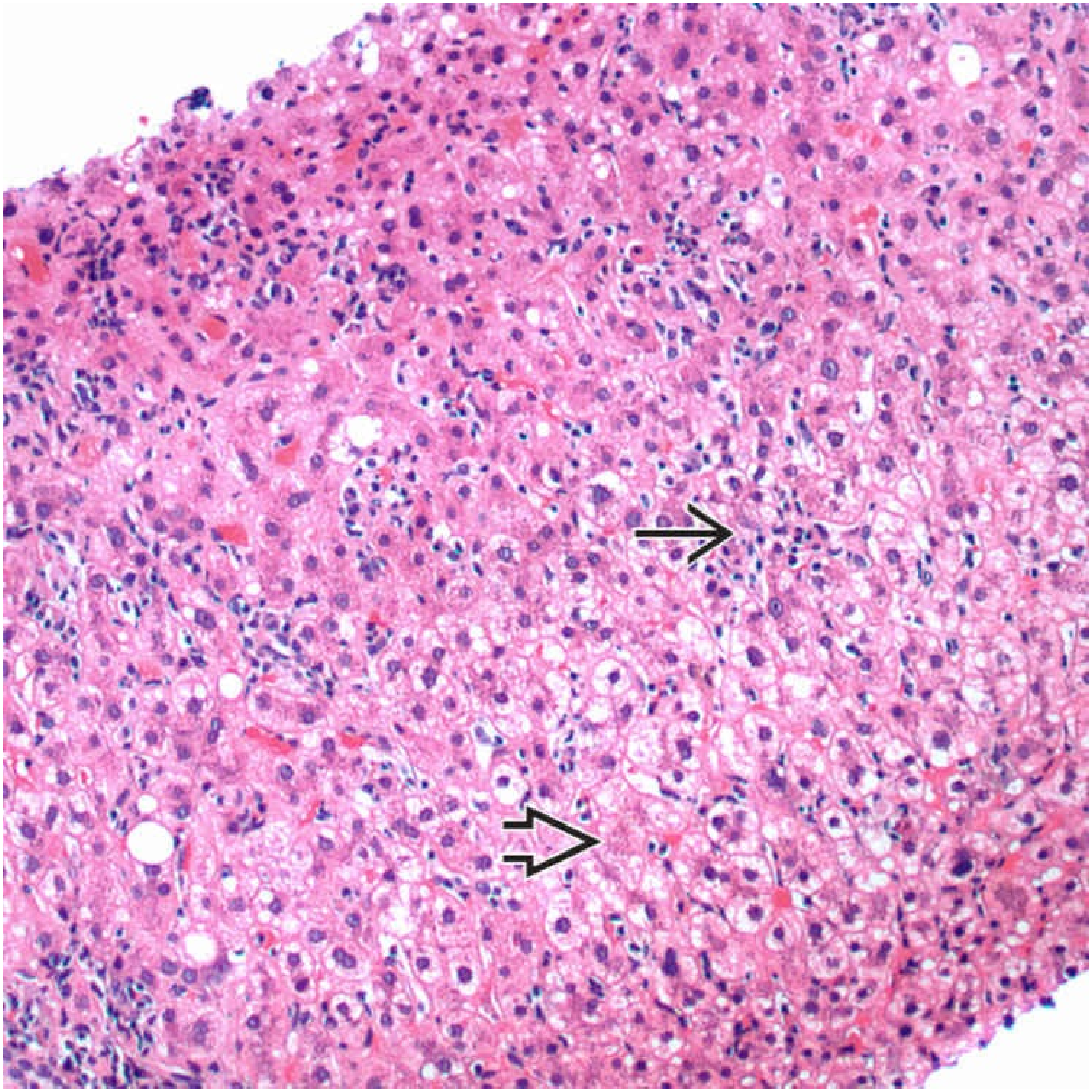
- Affects patients of all ages, predominantly women
  - Chronic disease by definition but may present clinically as acute or fulminant hepatitis
  - Ongoing hepatic injury and scarring with development of cirrhosis and end-stage liver disease
- Many patients have concurrent autoimmune diseases affecting other organs
- Laboratory tests
  - Elevated transaminases
  - Serum autoantibodies
  - Polyclonal hypergammaglobulinemia
- 1st-line therapy is immunosuppression with corticosteroids in combination with azathioprine
  - Most patients improve dramatically with treatment
    - 65% of patients achieve clinical, biochemical, and histologic remission within 3 years
- Liver transplantation indicated for patients with fulminant hepatitis or decompensated end-stage disease

Microscopic

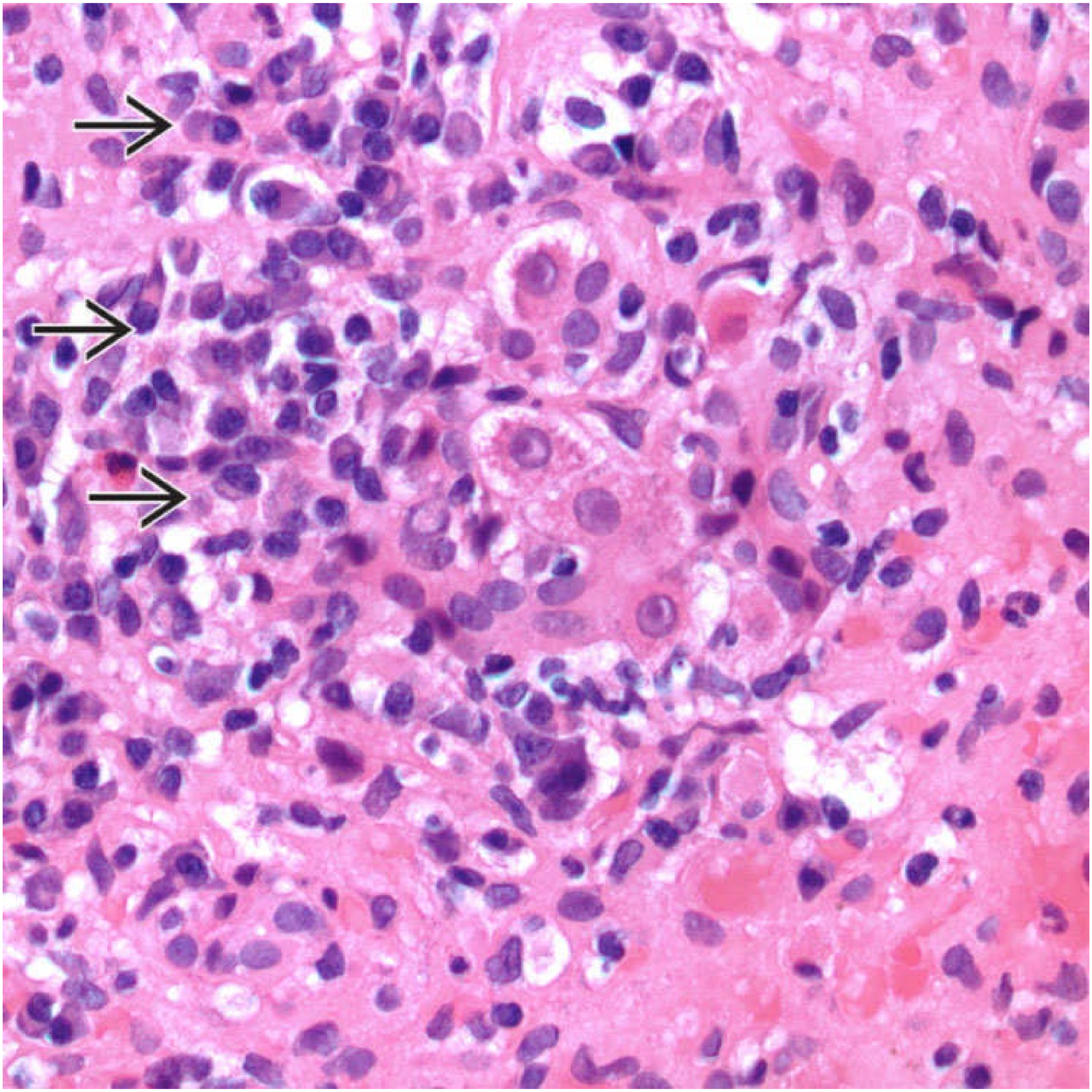
- Untreated autoimmune hepatitis (AIH) usually presents chronic hepatitis with marked interface activity and lobular injury
- Plasma cells may be prominent but are not constant feature of AIH
- Treated disease may present with normal biopsy or mild chronic hepatitis without specific histologic features
- Severe AIH may mimic acute viral hepatitis
- Extent of inflammation and injury (“grade”) and scarring (“stage”) may be scored



Portal Infiltrates
Typical portal inflammatory cell infiltrates in autoimmune hepatitis (AIH) contain large numbers of plasma cells. Periportal interface activity →, or “piecemeal necrosis,” is also a characteristic feature.

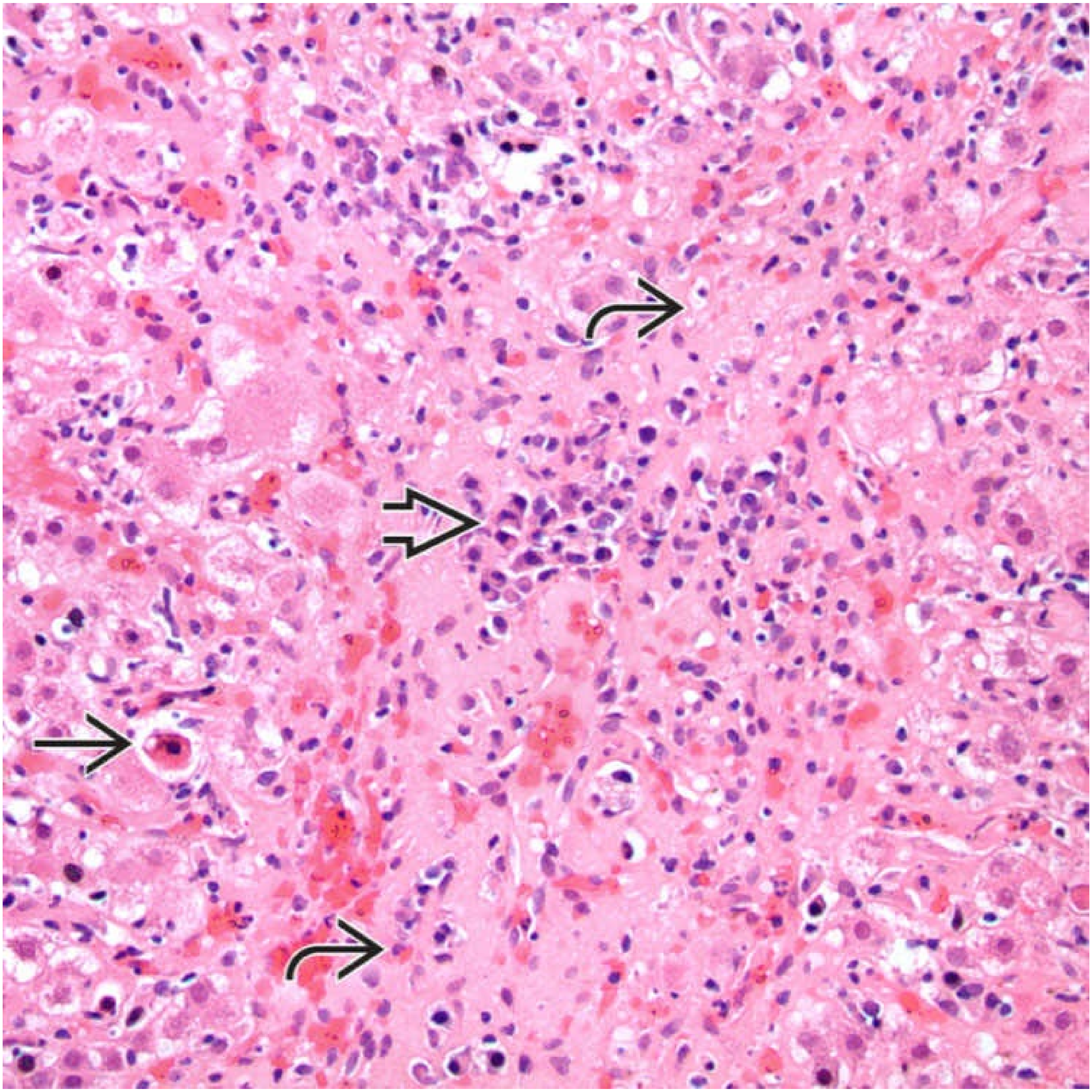


Lobular Injury
Diffuse lobular injury with inflammation →, hepatocyte swelling ⇨, and necrosis is characteristic of AIH.



Prominent Plasma Cells

Prominent lobular inflammatory cell infiltrates with large numbers of plasma cells → and hepatocyte injury are seen in this case of AIH.



Bridging Necrosis
Both single-cell necrosis and areas of confluent or “bridging” necrosis are seen in this case of AIH. Plasma cells are prominent.

TERMINOLOGY

Abbreviations

- Autoimmune hepatitis (AIH)

Synonyms

- Lupus/lupoid hepatitis

- Plasma cell hepatitis

Definitions

- Ongoing hepatitis presumed autoimmune in etiology
  - 3 types, based on identification of serum autoantibodies
  - ○ Type 1
    – Most common form
    – Antinuclear antibodies (ANA) &/or antismooth muscle antibodies (SMA)
    – Bimodal age distribution with peaks from 10-20 and 45-70 years of age

○ Type 2
– Antiliver/antikidney microsomal antibodies (anti-LKM-1)
– Most commonly affects children (ages 2-14) but also affects adults
– More severe disease with greater frequency of relapse
○ Type 3
– Soluble liver antigen (anti-SLA) or liver pancreas antigen (LP) antibodies
– Usually affects adults aged 30-50
○ Subtyping of AIH is of descriptive value only and has no bearing on disease management

ETIOLOGY/PATHOGENESIS

Inciting Event Unknown

- May include infectious agents, drugs, or toxins
- Ongoing immune-mediated liver cell destruction

CLINICAL ISSUES

Epidemiology

- Incidence
  - ○ 0.1-1.0 per 100,000 per year in North American and European populations
- Age
  - ○ Affects patients of all ages, including children and adolescents
- Sex
  - ○ Strong female predominance
    – M:F = 1:4
- Ethnicity
  - ○ All ethnicities affected

Presentation

- Chronic disease by definition but may present clinically as acute or fulminant hepatitis
  - Patients with acute onset of symptoms often found to have clinical, laboratory, &/or histologic signs of chronic liver disease
  - Acute presentation may represent flare of previously subclinical disease
  - Some patients have no evidence of chronic liver disease, appear clinically similar to acute viral or drug-related hepatitis
- Common signs and symptoms
  - Fatigue and lethargy
  - Upper abdominal discomfort
  - Hepatomegaly
  - Jaundice
- Many patients have concurrent autoimmune diseases affecting other organs

Laboratory Tests

- Elevated transaminases, often markedly so
  - Hyperbilirubinemia may be seen but is usually mild
  - Serum autoantibodies
  - ANA
  - SMA
  - LKM-1
  - Perinuclear antineutrophil cytoplasm (p-ANCA) in type 1 AIH only
- Polyclonal hypergammaglobulinemia

Natural History

- Progressive disease
  - Ongoing hepatic injury and scarring with development of cirrhosis and end-stage liver disease

Treatment

- Surgical approaches
  - Liver transplantation indicated for patients with fulminant hepatitis, end-stage disease with decompensation, or hepatocellular carcinoma
  - Recurrent AIH occurs in 20-30% of patients
- Drugs
  - 1st-line therapy is corticosteroids in combination with azathioprine
  - Treatment reduces disease activity and improves survival
    - 65% of patients achieve clinical, biochemical, and histologic remission within 3 years
    - Histologic, symptomatic, and biochemical improvement in 80% of patients
    - Improves patient 5-year survival from 40% to > 90%
  - Over time, treatment regimen managed to minimize disease activity and mitigate medication side effects

Prognosis

- Prognosis mainly relates to severity of hepatitis at initial presentation
  - Most patients improve dramatically with immunosuppressive therapy
  - Small percentage of compliant patients worsen despite therapy
  - Failure to respond is associated with early age at onset, acute or fulminant presentation, and hyperbilirubinemia
- Decompensated liver disease, ascites, or hepatic encephalopathy predicts poor prognosis
- Progressive disease associated with increasing fibrosis, ultimately leading to cirrhosis and liver failure

MICROSCOPIC

Histologic Features

- Dense portal inflammatory cell infiltrates
  - Mostly comprised of lymphocytes and plasma cells
  - Plasma cells may be prominent, present in large sheets or clusters
  - Plasma cells are typical but not constant feature of AIH
- Interface activity
  - Defined as inflammation extending beyond portal tract, crossing limiting plate, and inciting hepatocyte injury or necrosis
    - Also termed "piecemeal necrosis" because hepatocytes undergo necrosis in piecemeal fashion
  - Often prominent feature in untreated AIH but usually improves with immunosuppressive therapy
- Lobular inflammation and hepatocyte necrosis
  - May be severe, particularly in untreated patients
    - May see single-cell apoptosis ("acidophil bodies") or confluent necrosis
    - Areas of confluent hepatocyte necrosis may extend between adjacent lobules as "bridging necrosis"
  - Plasma cells may be prominent component of lobular inflammatory cell infiltrates but not invariably present
- Fibrosis
  - Portal-based fibrosis similar to that in other forms of chronic hepatitis
  - Fibrosis progresses in stellate or periportal fashion
  - Progressive fibrosis results in bridging fibrous septa between lobules and, ultimately, cirrhosis
  - In cases with extensive necrosis, collapse of reticulin framework should not be misinterpreted as fibrosis
    - Type 3 collagen of reticulin fibers stains pale gray-blue with trichrome
    - Type 1 collagen in fibrosis stains intense blue with trichrome
    - Residual areas of viable or regenerating hepatocytes should not be misinterpreted as cirrhotic nodules
- Perivenular parenchymal necrosis
  - Foci of inflammation and hepatocyte necrosis around central veins very characteristic of AIH
  - Sometimes termed "centrilobular piecemeal necrosis"
- Cholestasis
  - AIH may present as cholestatic hepatitis

    – Particularly in patients who present with acute onset
  - Bile duct damage or ductopenia are not features of AIH
- Giant cell transformation of hepatocytes
  - Numerous large multinucleated hepatocytes seen in selected cases (postinfantile giant cell hepatitis)
  - Nonspecific feature probably reflecting extensive hepatocyte injury and regeneration
- Treated disease may present with normal biopsy or mild chronic hepatitis without specific histologic features

DIFFERENTIAL DIAGNOSIS

Chronic Viral Hepatitis

- Distinguished by laboratory testing for viral vs. autoimmune markers
- Typically exhibits less severe interface activity and hepatocyte necrosis than untreated AIH

Primary Biliary Cholangitis

- Antimitochondrial antibody positive in > 90% of cases
- Bile duct injury, often with granulomas and ductopenia
- Absence of hepatocyte injury or necrosis
- Must distinguish from AIH because therapies differ

Drug-Induced Hepatitis

- Clinically distinguished based on autoimmune markers and presence of offending agent
- Medications may incite AIH-like syndrome, which may or may not abate after removal of drug

Overlap Syndromes

- Diagnosis requires clinical and histologic evidence of both diseases, either simultaneously or in succession
  - Minimal diagnostic criteria not well defined
  - Primary biliary cholangitis: Autoimmune hepatitis overlap syndrome
  - Need at least 2 of 3 specific features of each disease, with interface hepatitis mandatory
  – AIH features include ALT 5x normal, IgG 2x normal or ASMA, and moderate or severe piecemeal necrosis
  – PBC features are alkaline phosphatase 2x normal or GGT 5x normal, AMA, and florid duct lesion on biopsy
- Autoimmune hepatitis: Primary sclerosing cholangitis overlap syndrome
  - More common in pediatric patients

IgG4 Disease

- Features prominence of IgG4(+) plasma cells and variably elevated serum IgG4
  - Often affects multiple organs
  - Histologic criteria for liver disease not well defined

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- International Autoimmune Hepatitis Group proposed scoring system that reflects certainty of diagnosis
  - Weighted scoring system based on combination of histologic, clinical, and laboratory findings that either provide evidence in support of or against diagnosis of AIH
  - Largely used for research purposes
  - Rarely required for diagnosis in clinical practice

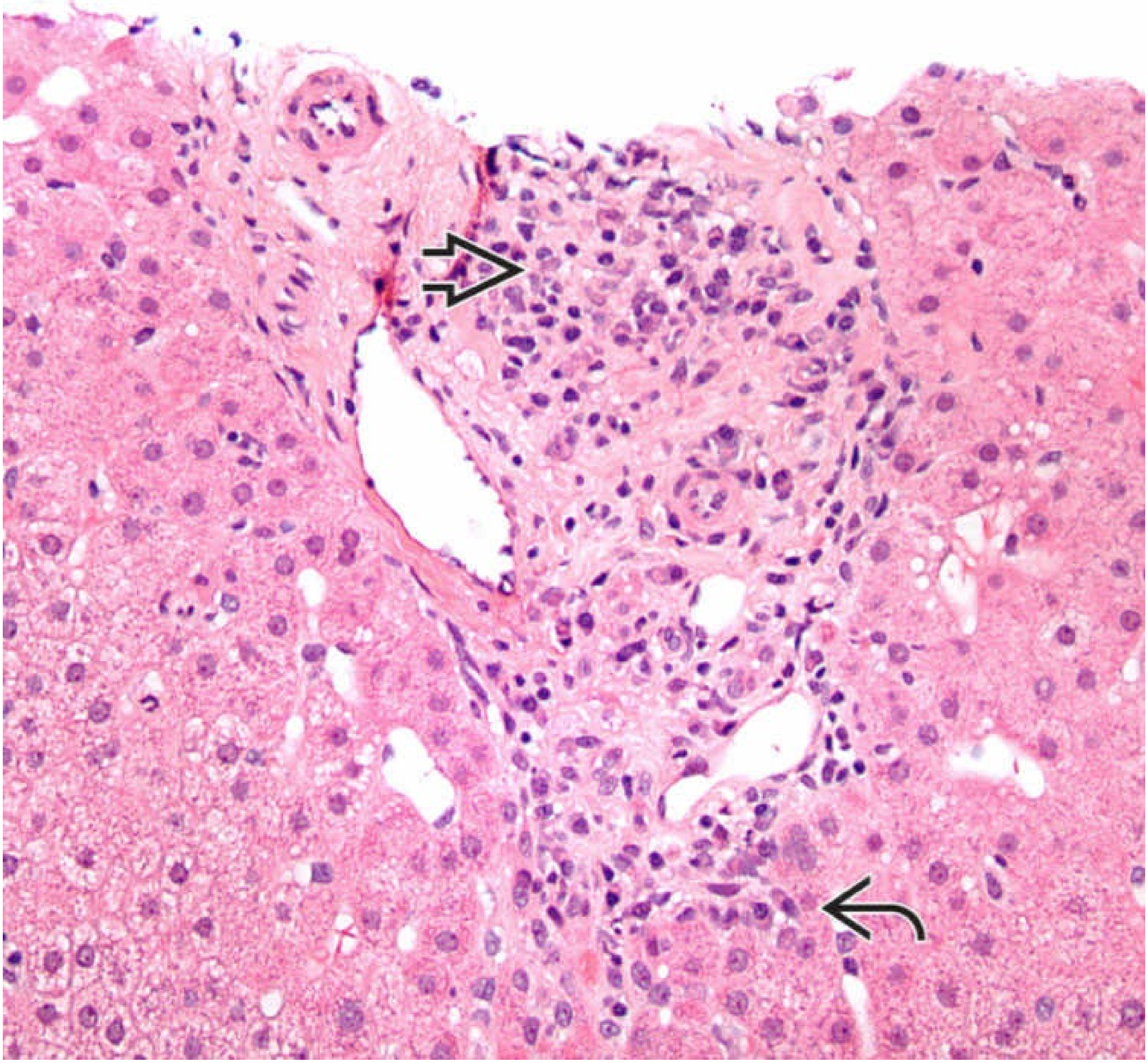
Pathologic Interpretation Pearls

- Untreated AIH usually presents chronic hepatitis with marked interface activity and lobular injury
  - Plasma cells may be prominent
- Severe AIH may exhibit more prominent lobular inflammation and injury, mimicking acute viral hepatitis
- Treated disease may present with normal biopsy or mild chronic hepatitis without specific histologic features

REPORTING

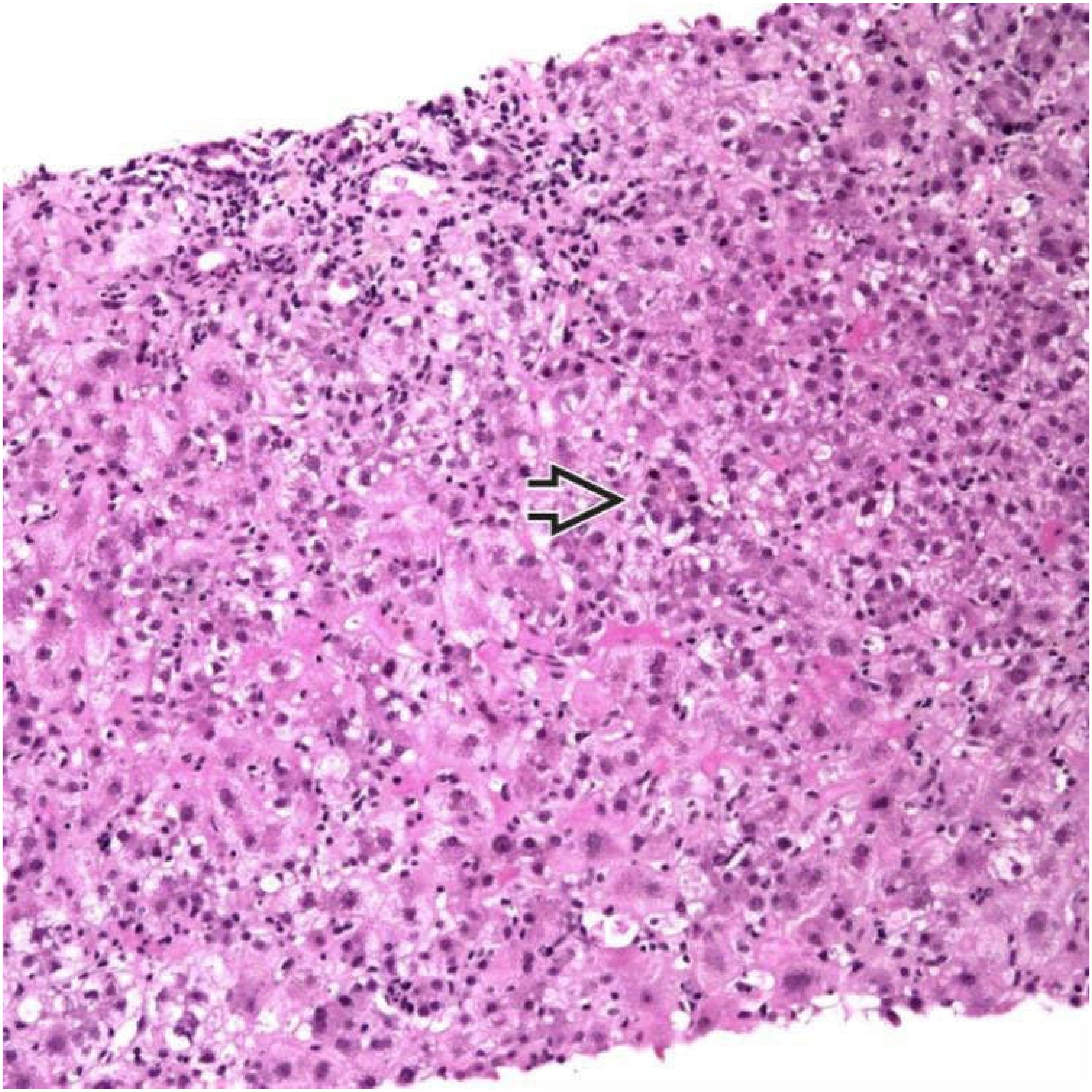
Scoring

- Severity of inflammation and injury and degree of scarring may be reported using systems for grading and staging chronic hepatitis
  - Batts and Ludwig, Ishak, Metavir or Knodell
- Grade: Severity and extent of necroinflammatory activity, defined as periportal interface activity and lobular inflammation and hepatocyte injury
- Stage: Extent of fibrosis, as assessed with Masson trichrome stain

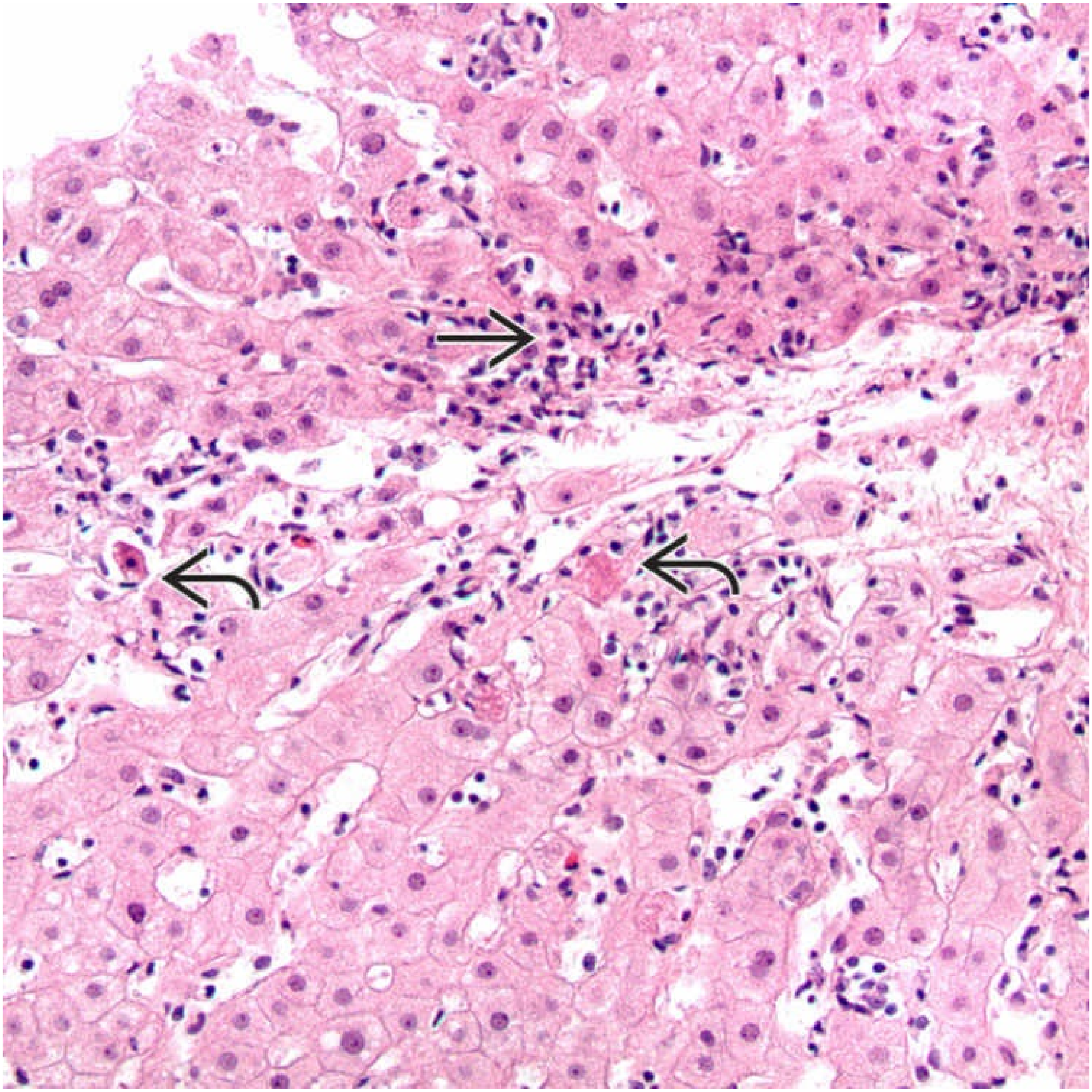


Portal Infiltrates

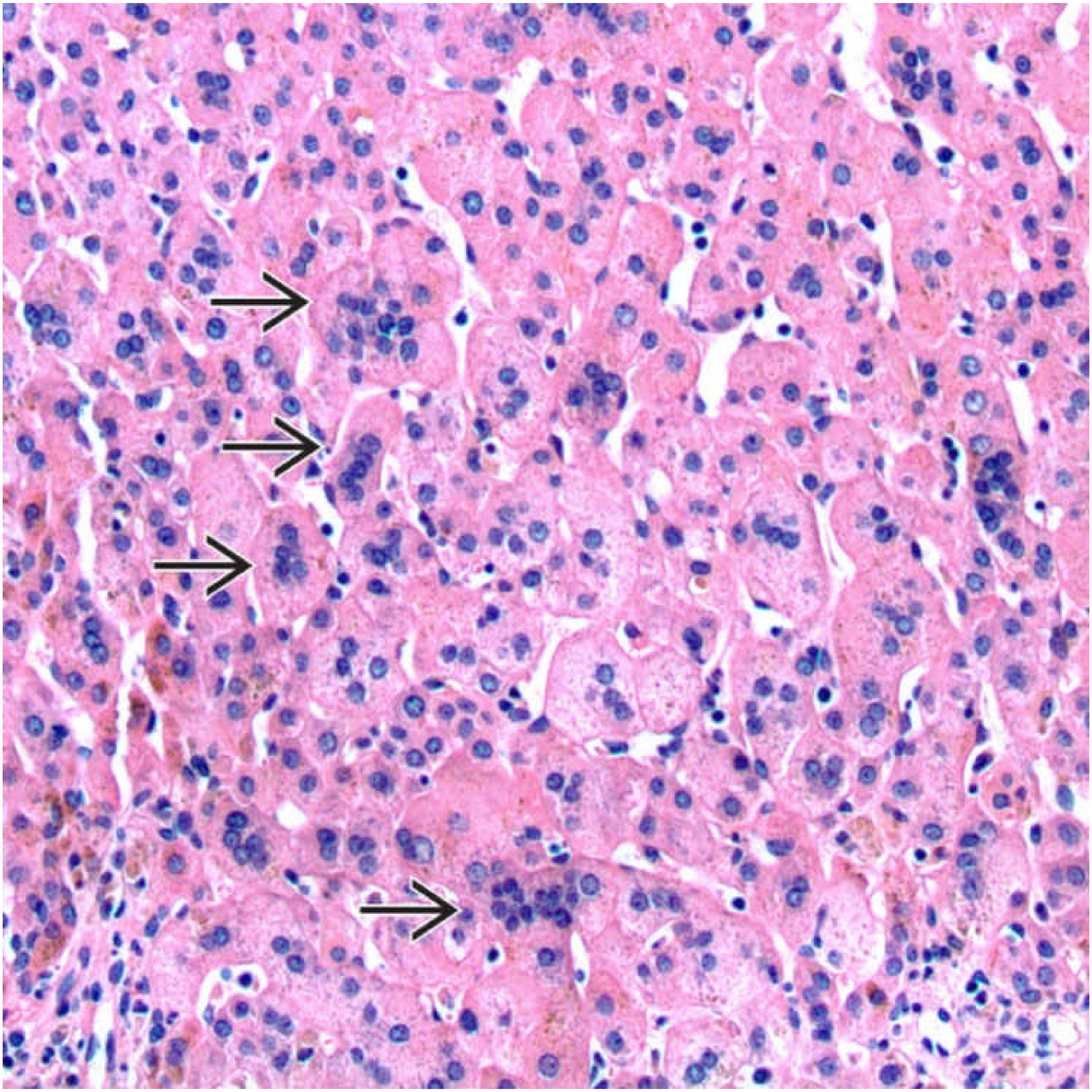
This case of AIH shows mild portal inflammation, including lymphocytes and numerous plasma cells. There is also interface activity. Plasma cells are a constant, but not invariable, feature.



Lobular Injury
This needle biopsy from a case of AIH shows lobular disarray, lymphoplasmacytic inflammation, hepatocyte rosette formation ⇨, and marked hepatocyte injury.

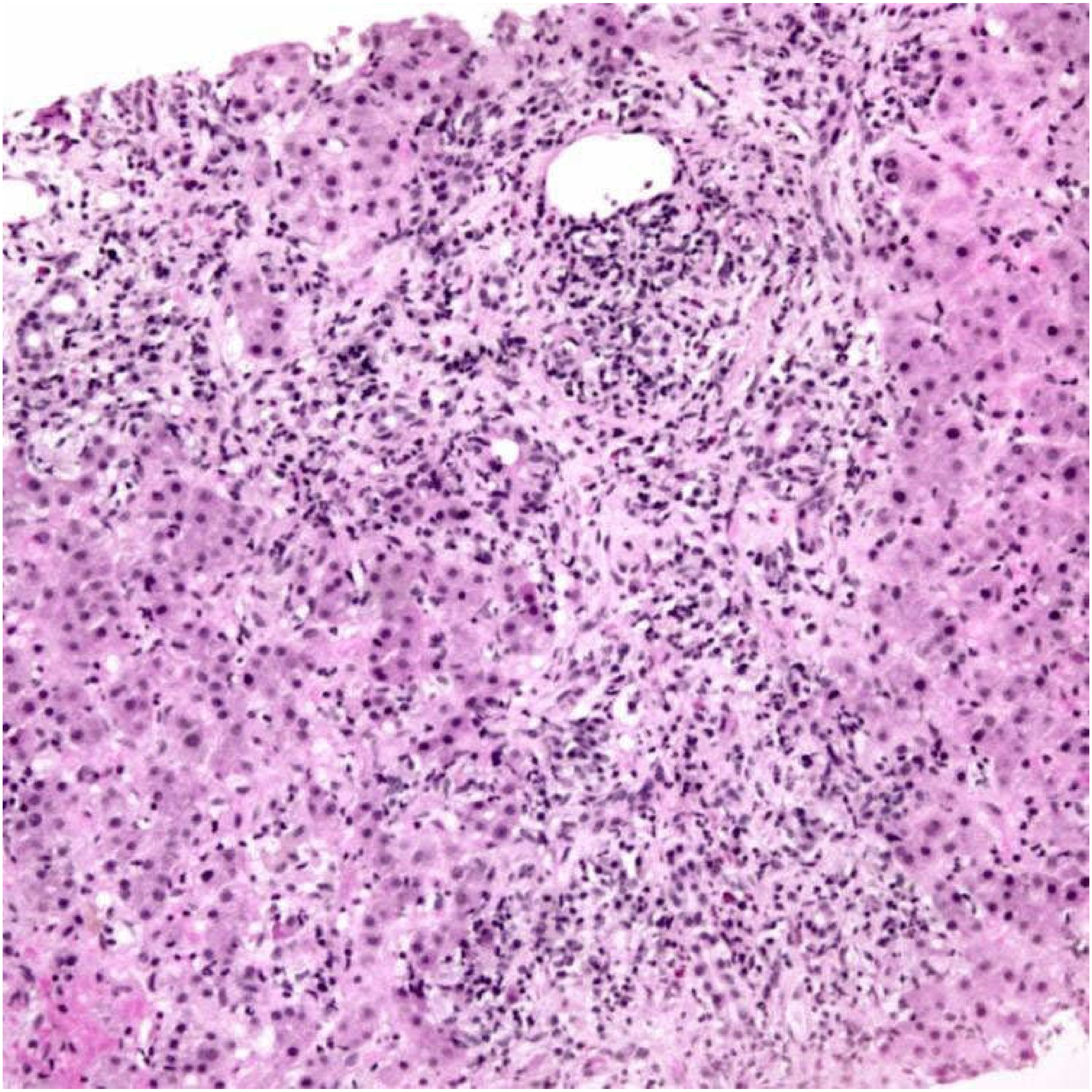


Centrilobular Piecemeal Necrosis
Inflammation → and necrosis ↷ located around the central vein, often referred to as “centrilobular piecemeal necrosis,” is a characteristic finding of AIH.

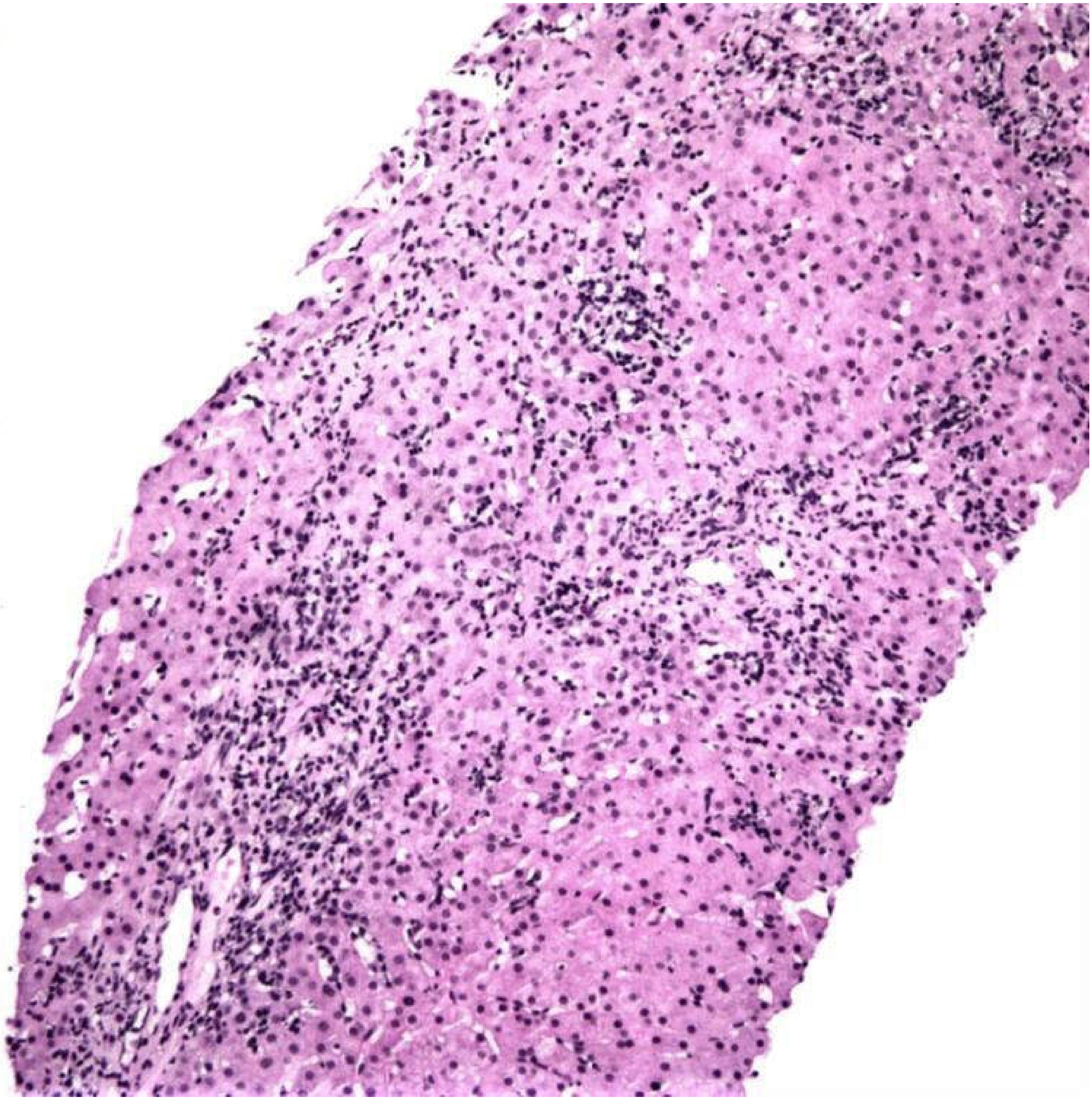


Giant Cell Change

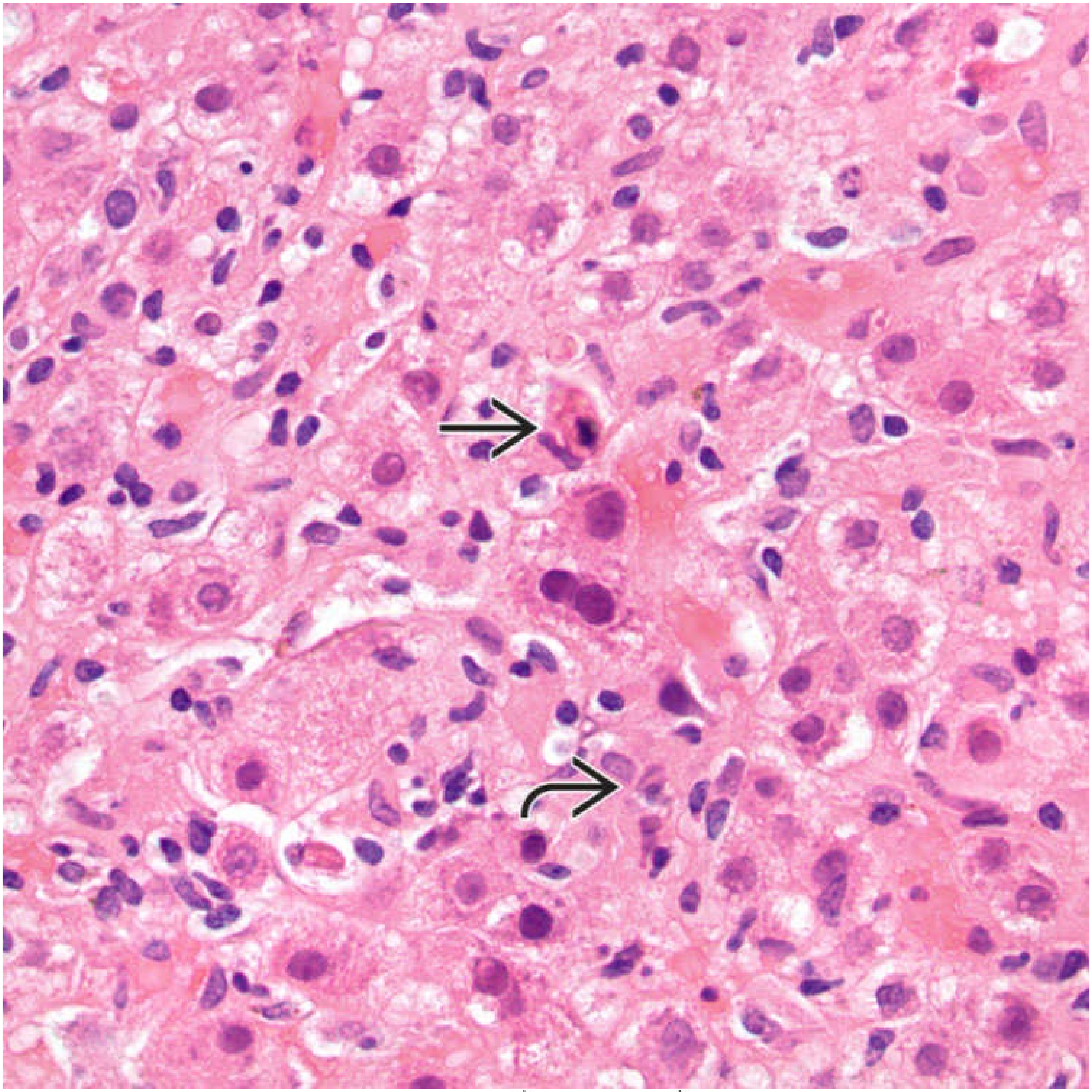
Numerous multinucleated hepatocytes → are present in this case of AIH. Also termed “postinfantile giant cell hepatitis,” this probably represents a nonspecific response to extensive hepatocyte injury.



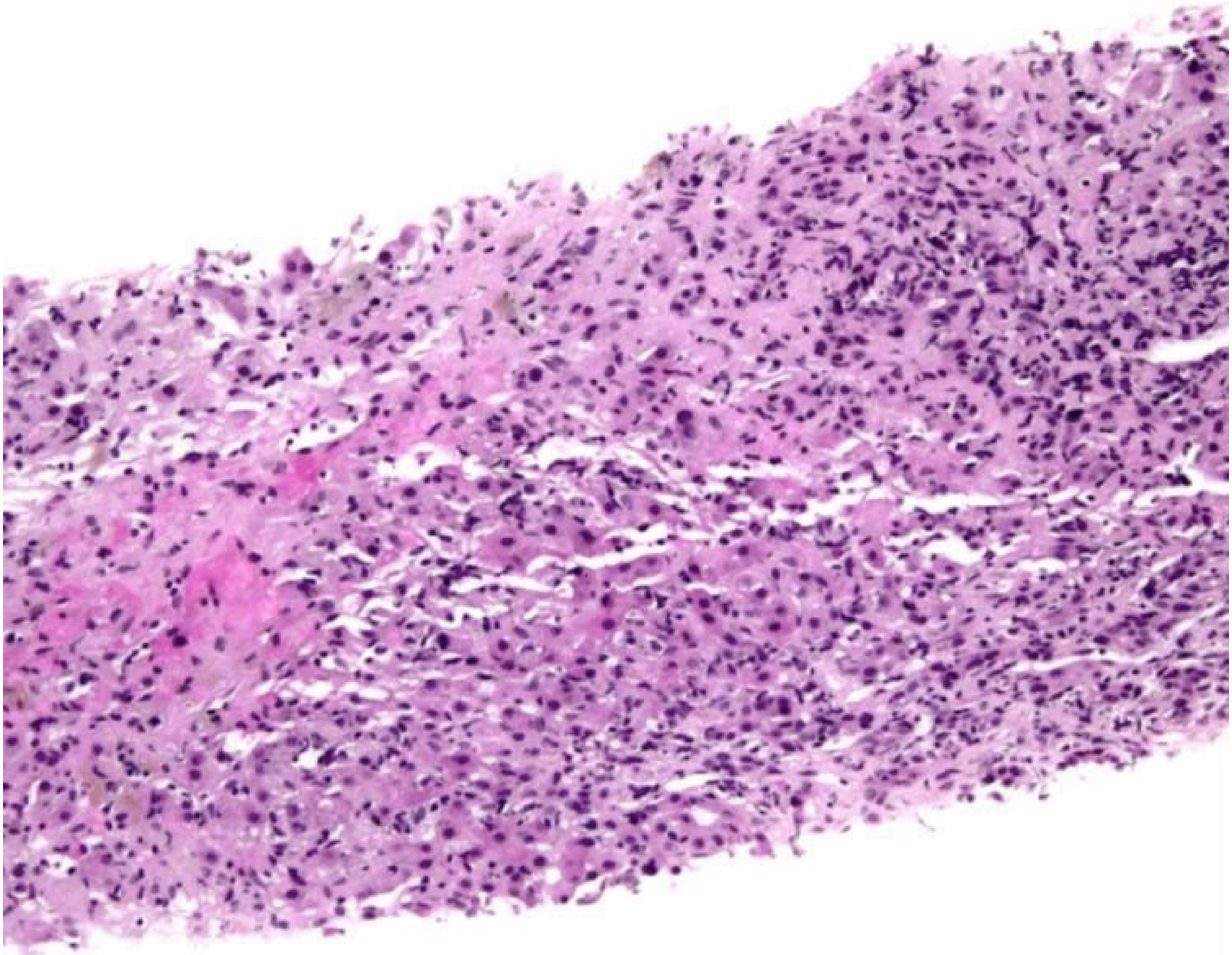
Portal Fibrosis
This example of AIH shows fibrous portal expansion, interface activity, and a lymphoplasmacytic infiltrate in the portal tract. Note the spillover of the inflammation into the lobule.



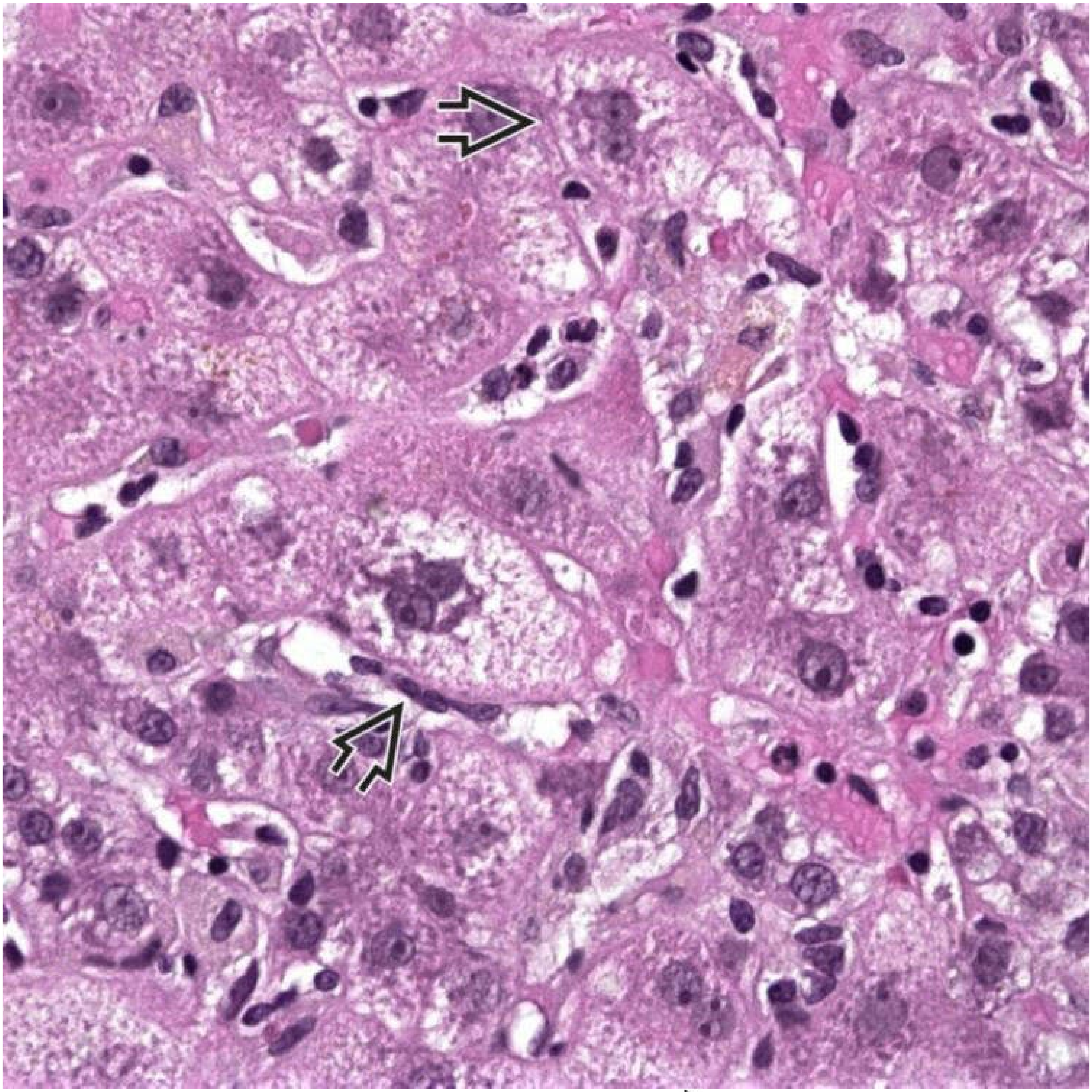
Autoimmune Hepatitis/PBC Overlap
This case of AIH/PBC overlap showed marked lobular and portal inflammation typical of AIH, but also featured interlobular bile duct injury and dropout.



H&E demonstrates spotty lobular inflammation ↱ and necrosis →, a common finding in autoimmune hepatitis.



This liver biopsy from a patient with autoimmune hepatitis shows necrosis and parenchymal collapse, with very little remaining viable hepatic parenchyma.



This high-power view shows feathery degeneration of hepatocytes ➪ in a case of autoimmune hepatitis.

SELECTED REFERENCES

1. Czaja, AJ. Diagnosis and management of autoimmune hepatitis. *Clin Liver Dis*. 2015; 19(1):57–79.
2. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune hepatitis. *J Hepatol*. 2015; 63(4):971–1004.
4. deLemos, AS, et al. Drug-induced liver injury with autoimmune features. *Semin Liver Dis*. 2014; 34(2):194–204.
7. Manns, MP, et al. Diagnosis and management of autoimmune hepatitis. *Hepatology*. 2010; 51(6):2193–2213.

13. Hennes, EM, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology*. 2008; 48(1):169–176.
14. Washington, MK. Autoimmune liver disease: overlap and outliers. *Mod Pathol*. 2007; 20(Suppl 1):S15–S30.

3. Czaja, AJ. Current and prospective pharmacotherapy for autoimmune hepatitis. *Expert Opin Pharmacother*. 2014; 15(12):1715–1736.
5. Floreani, A, et al. Autoimmune hepatitis: Contrasts and comparisons in children and adults – a comprehensive review. *J Autoimmun*. 2013; 46:7–16.
6. Yada, N, et al. Autoimmune hepatitis and immunoglobulin G4-associated autoimmune hepatitis. *Dig Dis*. 2013; 31(5-6):415–420.
8. Czaja, AJ, et al. Non-classical phenotypes of autoimmune hepatitis and advances in diagnosis and treatment. *World J Gastroenterol*. 2009; 15(19):2314–2328.
9. Czaja, AJ. Features and consequences of untreated type 1 autoimmune hepatitis. *Liver Int*. 2009; 29(6):816–823.
10. Mehendiratta, V, et al. Serologic markers do not predict histologic severity or response to treatment in patients with autoimmune hepatitis. *Clin Gastroenterol Hepatol*. 2009; 7(1):98–103.
11. Ramakrishna, J, et al. Long-term minocycline use for acne in healthy adolescents can cause severe autoimmune hepatitis. *J Clin Gastroenterol*. 2009; 43(8):787–790.
12. Verma, S, et al. Liver failure as initial presentation of autoimmune hepatitis: clinical characteristics, predictors of response to steroid therapy, and outcomes. *Hepatology*. 2009; 49(4):1396–1397.

Primary Biliary Cholangitis

KEY FACTS

Terminology

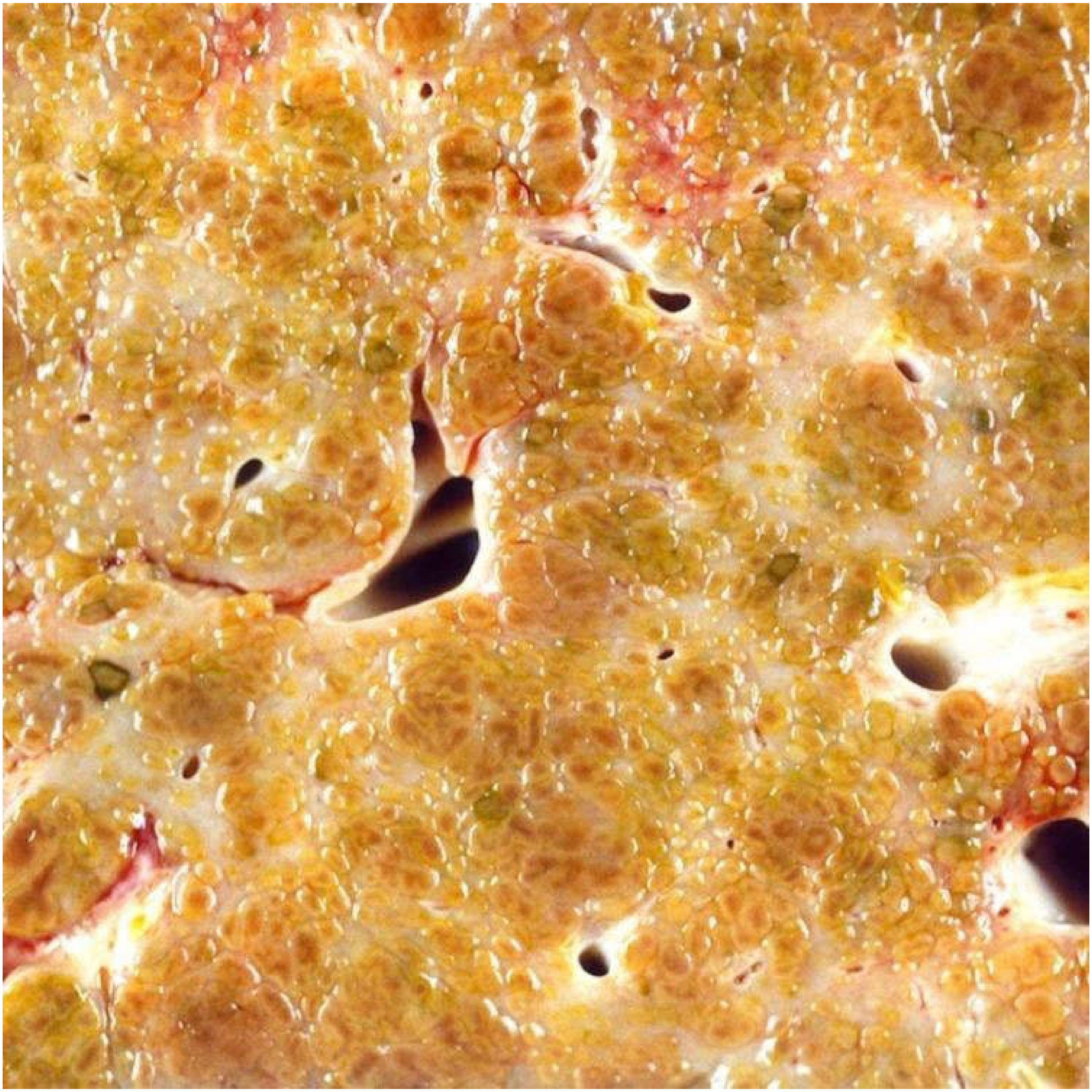
- Chronic cholestatic disease in which intrahepatic bile ducts are progressively destroyed by nonsuppurative inflammation

Clinical Issues

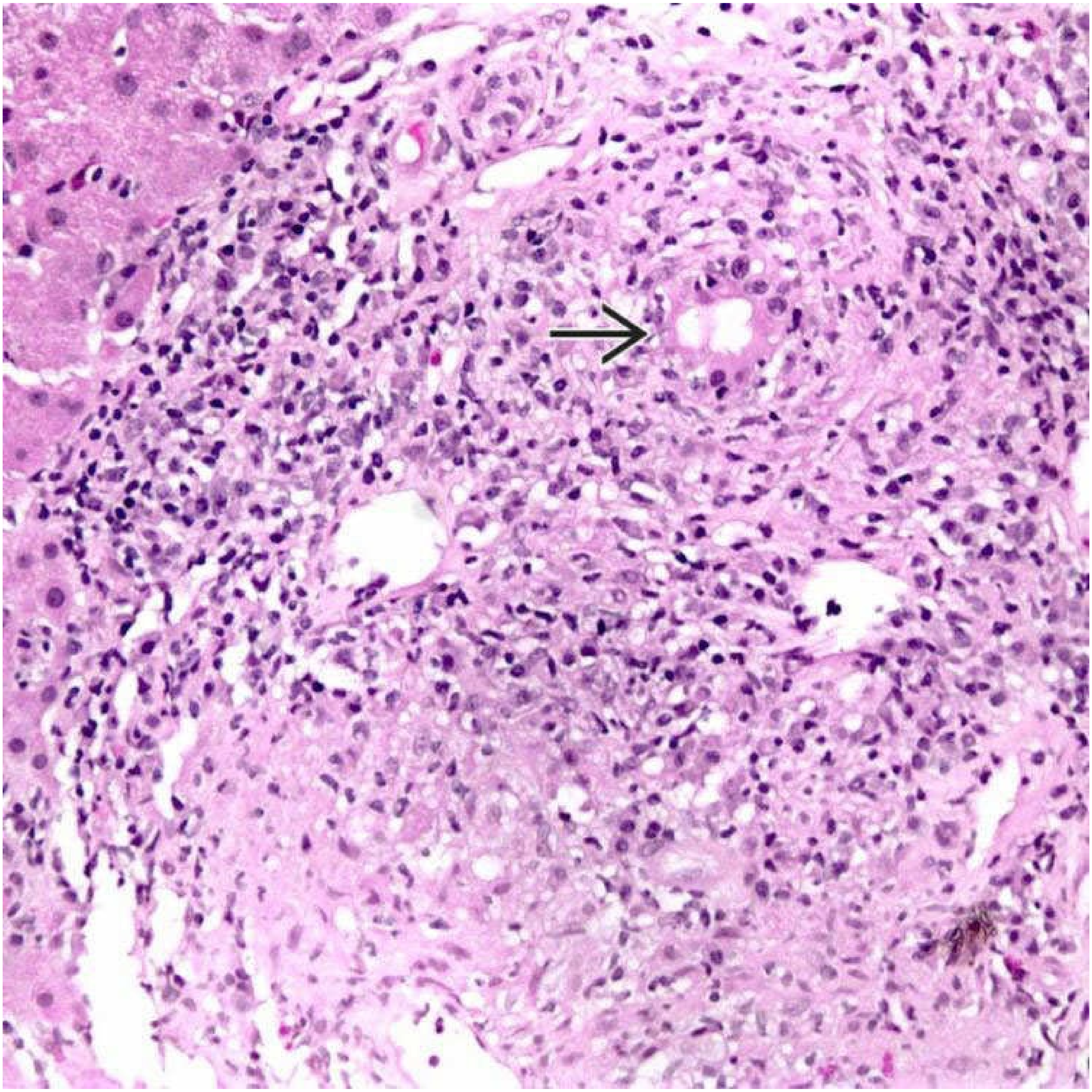
- Middle-aged to elderly women
  - > 90% of patients are female
  - Most common in individuals of North European descent
- Insidious onset with pruritus, fatigue, jaundice
  - Often other associated autoimmune disorders
- AMA(+)
  - Minority of cases are AMA(-)
- Elevation of GGT, alkaline phosphatase
  - Out of proportion to transaminases
- Ursodeoxycholic acid is treatment of choice
  - Not cure but delays progression in some patients

Microscopic

- Florid duct lesion with lymphocytic cholangitis and bile duct injury
  - Granulomatous inflammation variably present
- Biliary epithelial disarray with irregularly sized and pseudostratified nuclei and vacuolated, swollen cytoplasm
- Bile ductular reaction
- Cholate stasis
  - Copper stain highlights accumulated copper in hepatocytes
- Initially portal-based fibrosis, eventually forms portal-portal bridges
  - Cirrhosis is biliary type with irregular nodules (so-called jigsaw puzzle pattern)
- 4 histologic stages ranging from portal involvement to cirrhosis

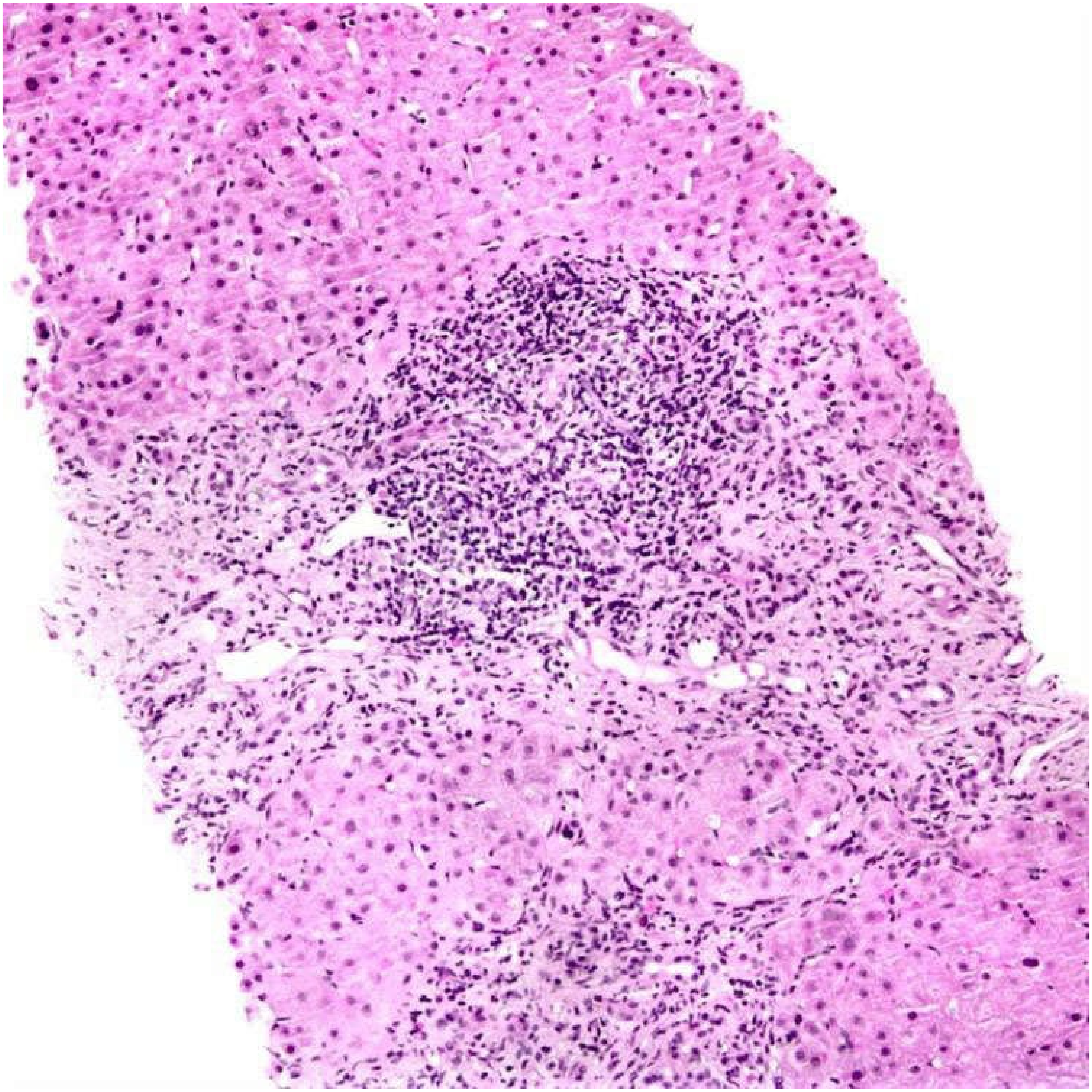


Gross Specimen
This photograph of the cut surface of a liver explanted for primary biliary cholangitis (PBC) emphasizes the green discoloration of the cirrhotic nodules, indicative of chronic cholestasis.



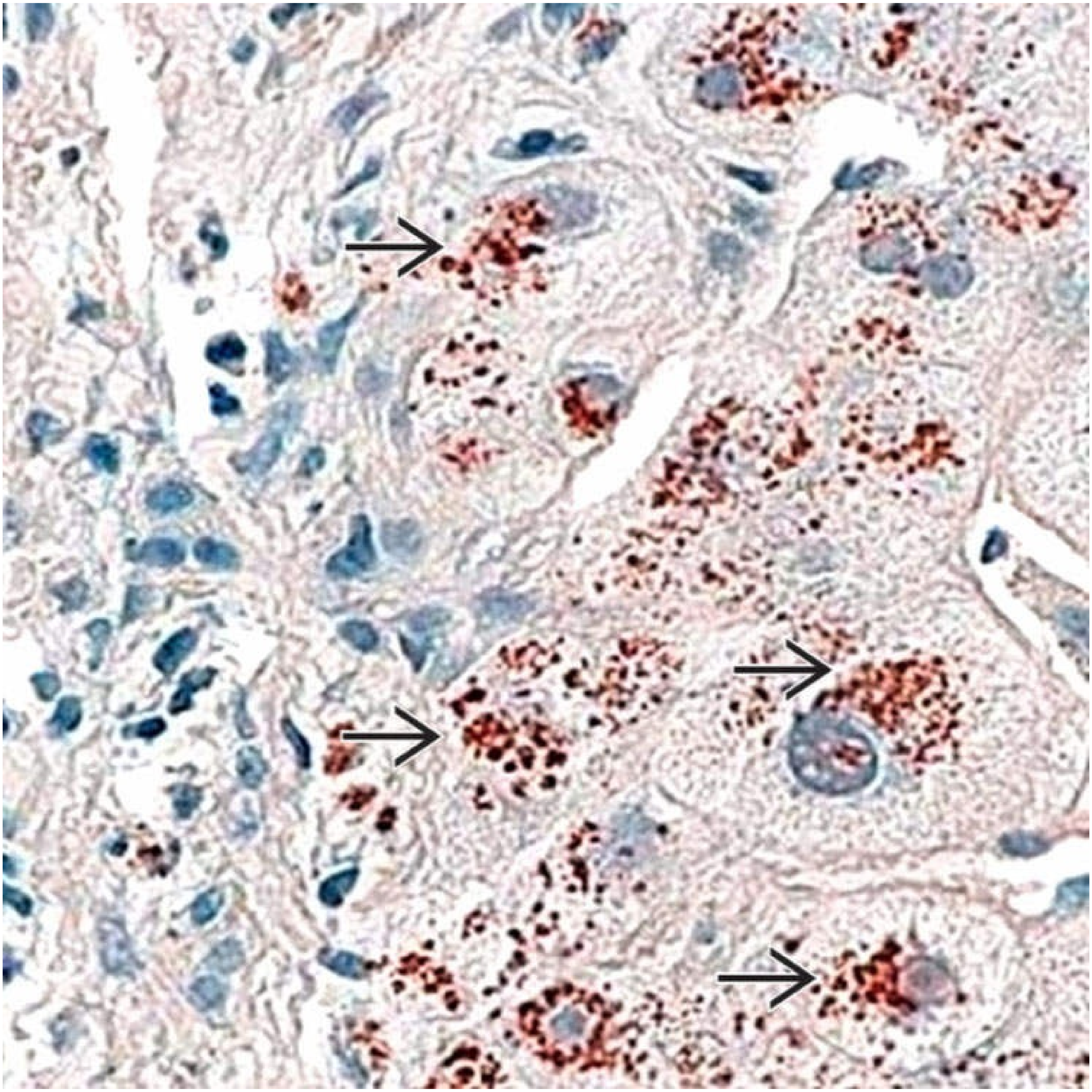
Florid Duct Lesion

This example of a florid duct lesion shows lymphocytic cholangitis in the interlobular bile duct → along with a nodular portal lymphoplasmacytic infiltrate and a granulomatous inflammation.



Portal Tract Changes

This biopsy from a patient with PBC shows nodular lymphoplasmacytic inflammation and lymphocytic cholangitis, even at low power. Fibrous expansion of the portal tract is also present. Similar histologic changes are also characteristic of AMA PBC (autoimmune cholangitis).



Copper Stain
The copper stain highlights changes of chronic cholestasis consisting of periportal orange-red granules → in the hepatocytes in PBC.

TERMINOLOGY

Abbreviations

- Primary biliary cirrhosis/cholangitis (PBC)
  - Cholangitis is recently preferred term

Definitions

- Chronic cholestatic disease in which intrahepatic bile ducts are progressively destroyed by nonsuppurative inflammation

ETIOLOGY/PATHOGENESIS

Unknown

- Probable autoimmune etiology

CLINICAL ISSUES

Epidemiology

- Incidence
  - Most common in individuals of North European descent
    - Typically 40-60 years of age
    - > 90% of patients are female

Presentation

- Insidious onset with pruritus (most common), fatigue, jaundice, associated autoimmune disorders

Laboratory Tests

- AMA(+)
- Elevation of GGT &/or alkaline phosphatase out of proportion to transaminases, which are typically mildly elevated or normal
- Elevated bilirubin, usually late in disease
- Elevated IgM

Treatment

- Ursodeoxycholic acid
  - Not cure but delays progression in some patients
- Liver transplant for advanced or decompensated disease

Prognosis

- Chronic, progressive disease

MICROSCOPIC

Histologic Features

- Florid duct lesion/destructive cholangitis

- Portal-based nodular inflammation composed of lymphocytes, plasma cells, eosinophils, macrophages
  - – Interface hepatitis may be present in some cases, resembling chronic hepatitis
- Bile duct injury
  - – Disrupted basement membrane
  - – Biliary epithelial disarray with irregularly sized and pseudostratified nuclei and vacuolated, swollen cytoplasm
  - – Eventual loss of interlobular bile ducts
- Lymphocytic cholangitis
  - – Granulomas variably present

• Bile ductular reaction
• Fibrosis
  - Initially portal, eventually forms portal-portal bridges
  - Cirrhosis is biliary type with irregular nodules (so-called jigsaw puzzle pattern)

• Chronic cholestasis
  - Swollen and rarefied hepatocytes adjacent to portal tracts (cholate stasis)
    - – Copper stain highlights copper in hepatocytes

• 4 histologic stages ranging from portal involvement to cirrhosis

DIFFERENTIAL DIAGNOSIS

Primary Sclerosing Cholangitis

• Predominantly men, associated with chronic idiopathic inflammatory bowel disease
• AMA(-); characteristic cholangiographic findings

Large Bile Duct Obstruction

• AMA(-)
• Lack florid duct lesion, progressive duct destruction, cholate stasis

Drug-Induced Cholestasis/Duct Injury

• Medication history

Infection

• Special stains necessary to exclude infection when granulomas are present

Sarcoidosis

• Systemic involvement; elevated angiotensin converting enzyme

Chronic Viral Hepatitis

• Bile duct damage/lymphocytic cholangitis is common, especially in hepatitis C (Poulsen lesion)
• AMA(-); viral serology or quantitative PCR (+)

Autoimmune Hepatitis

• Lack of florid duct lesion, bile duct damage/lymphocytic cholangitis
• More active lobular inflammation ± hepatocyte necrosis
• Transaminases typically significantly elevated

Autoimmune Hepatitis-PBC Overlap Syndrome

• < 10% of PBC patients; laboratory and histologic features of both autoimmune hepatitis and PBC
• Combination therapy with ursodeoxycholic acid and immunosuppression may be indicated

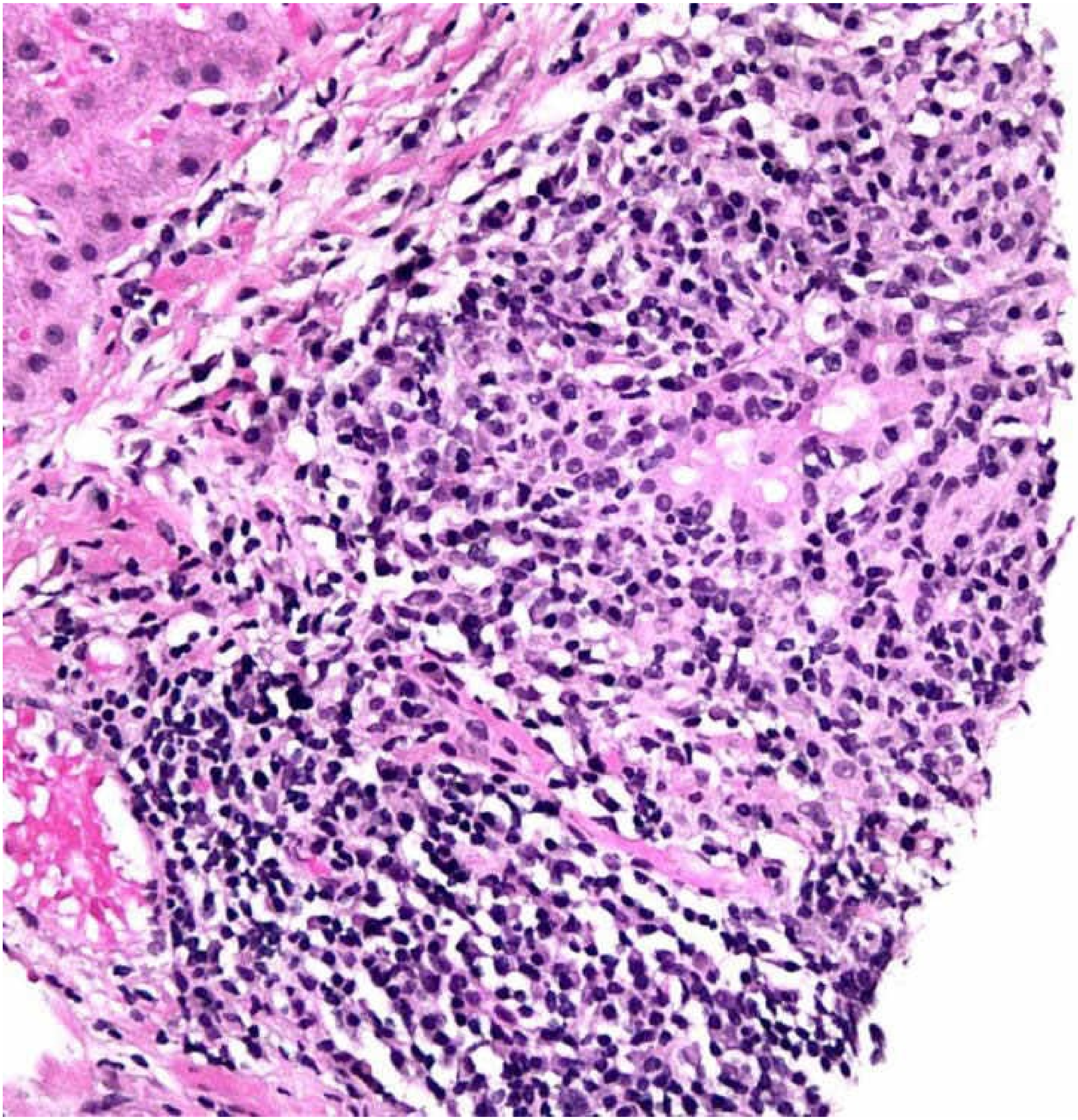
Autoimmune Cholangitis/AMA(-) PBC

• AMA(-), otherwise histology resembles PBC histologically and clinically

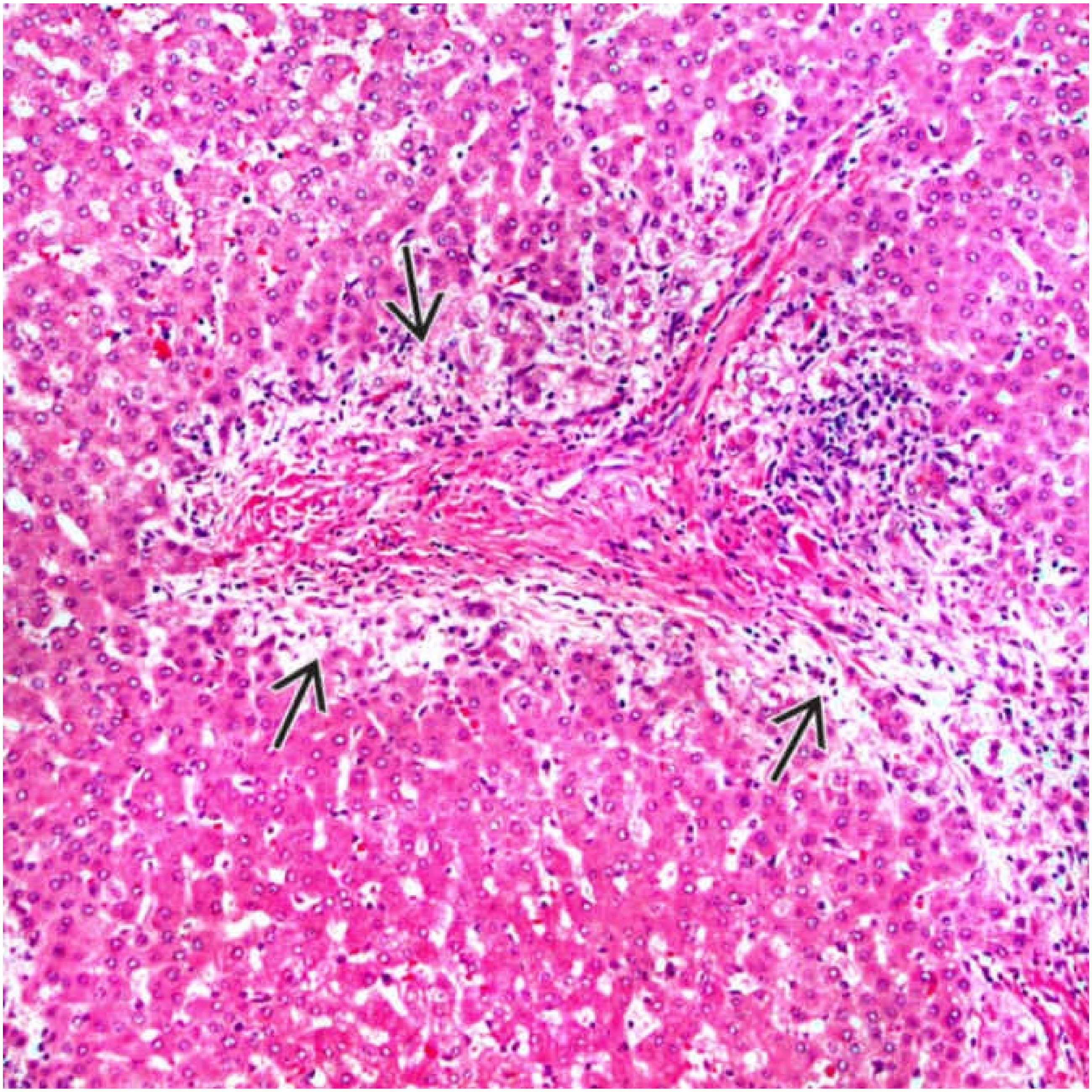
DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

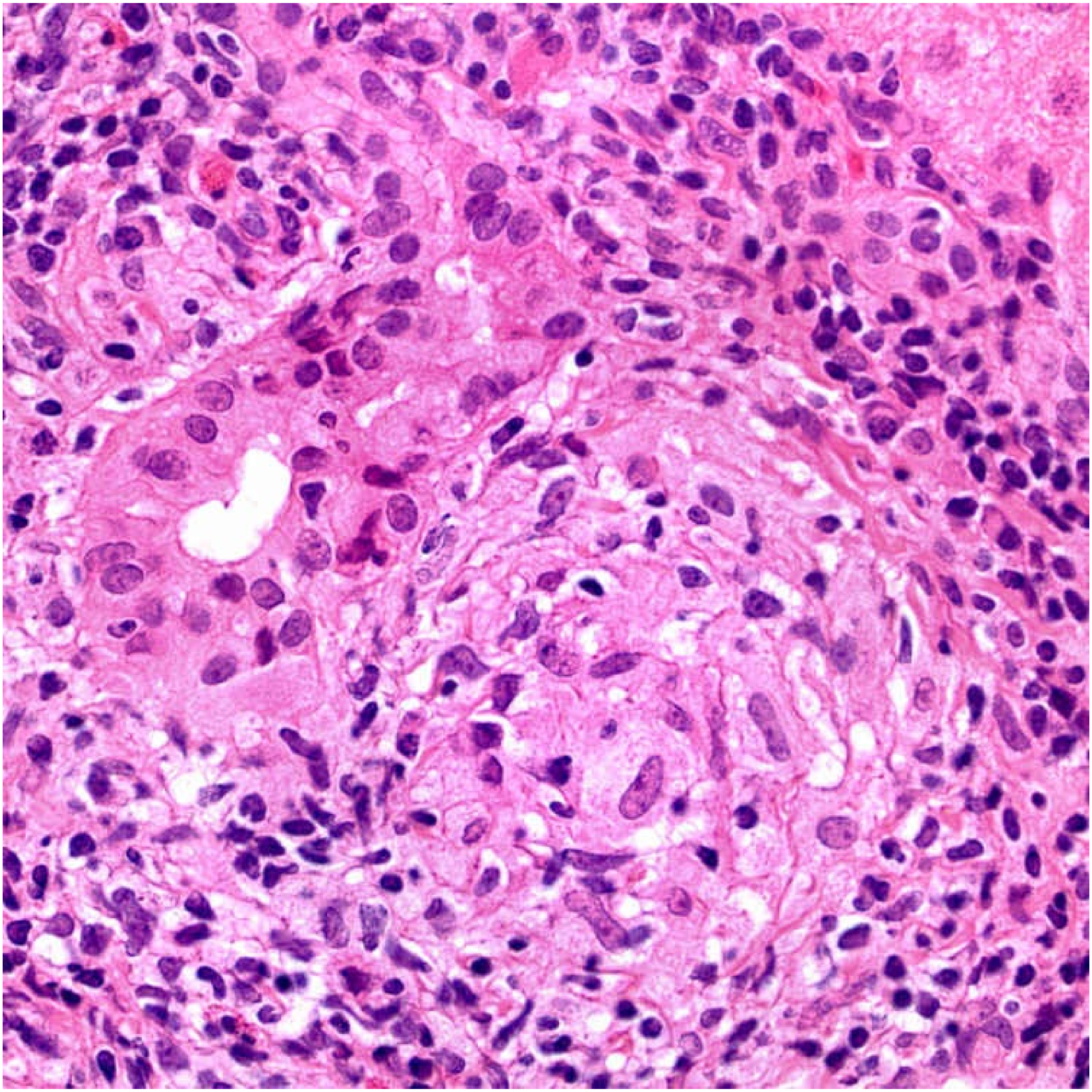
• Florid duct lesion
• Loss of interlobular bile ducts



Bile Duct Changes
PBC typically features a nodular lymphoplasmacytic infiltrate expanding the portal tract. Lymphocytic cholangitis and biliary epithelial damage are also present. Stage 1 PBC features portal hepatitis and florid duct lesions, as seen here.

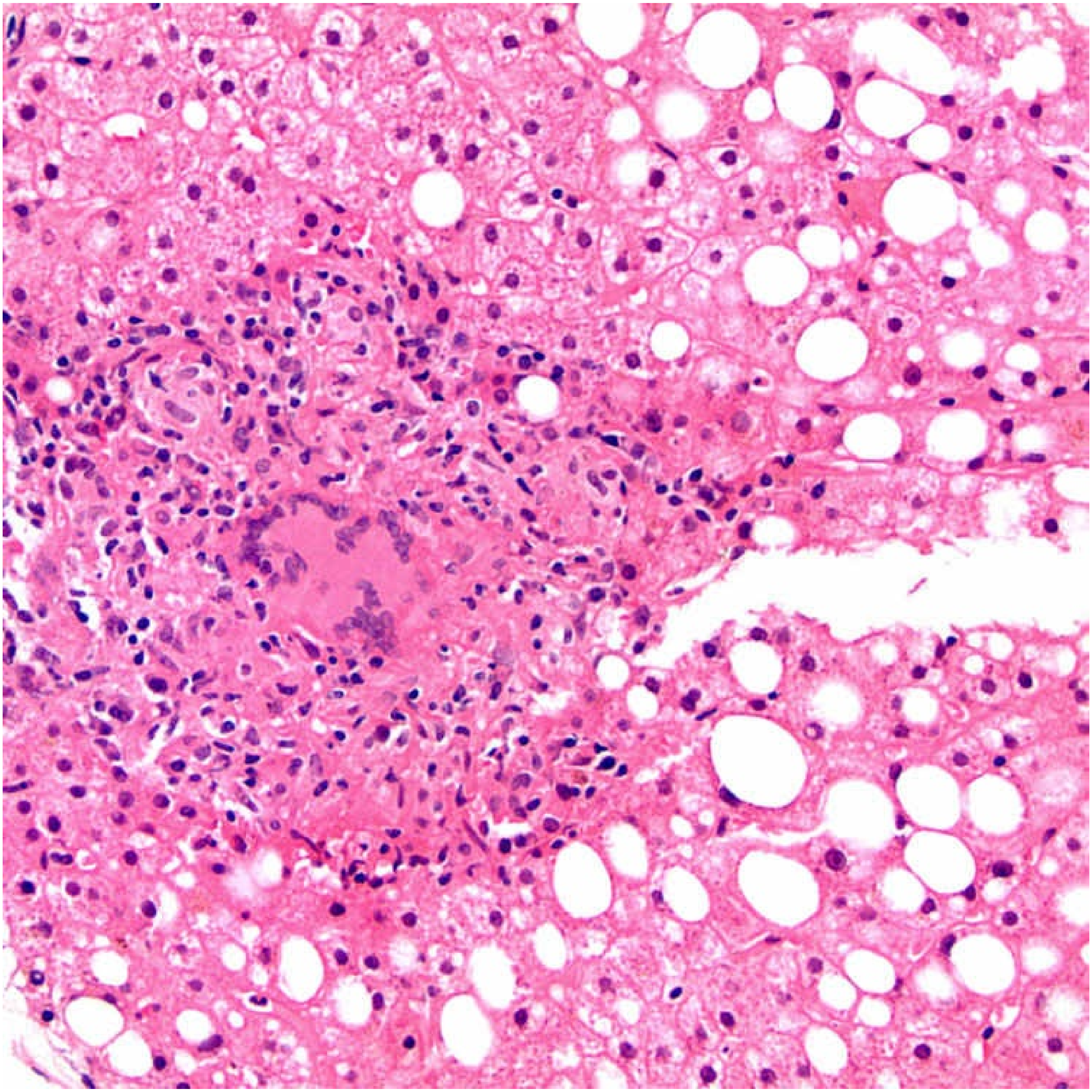


Cholate Stasis
Cholate stasis, a histologic feature indicating chronic cholestasis, is characterized by rarefied and swollen hepatocytes → adjacent to the portal tracts. Note the absence of the interlobular bile duct as well.



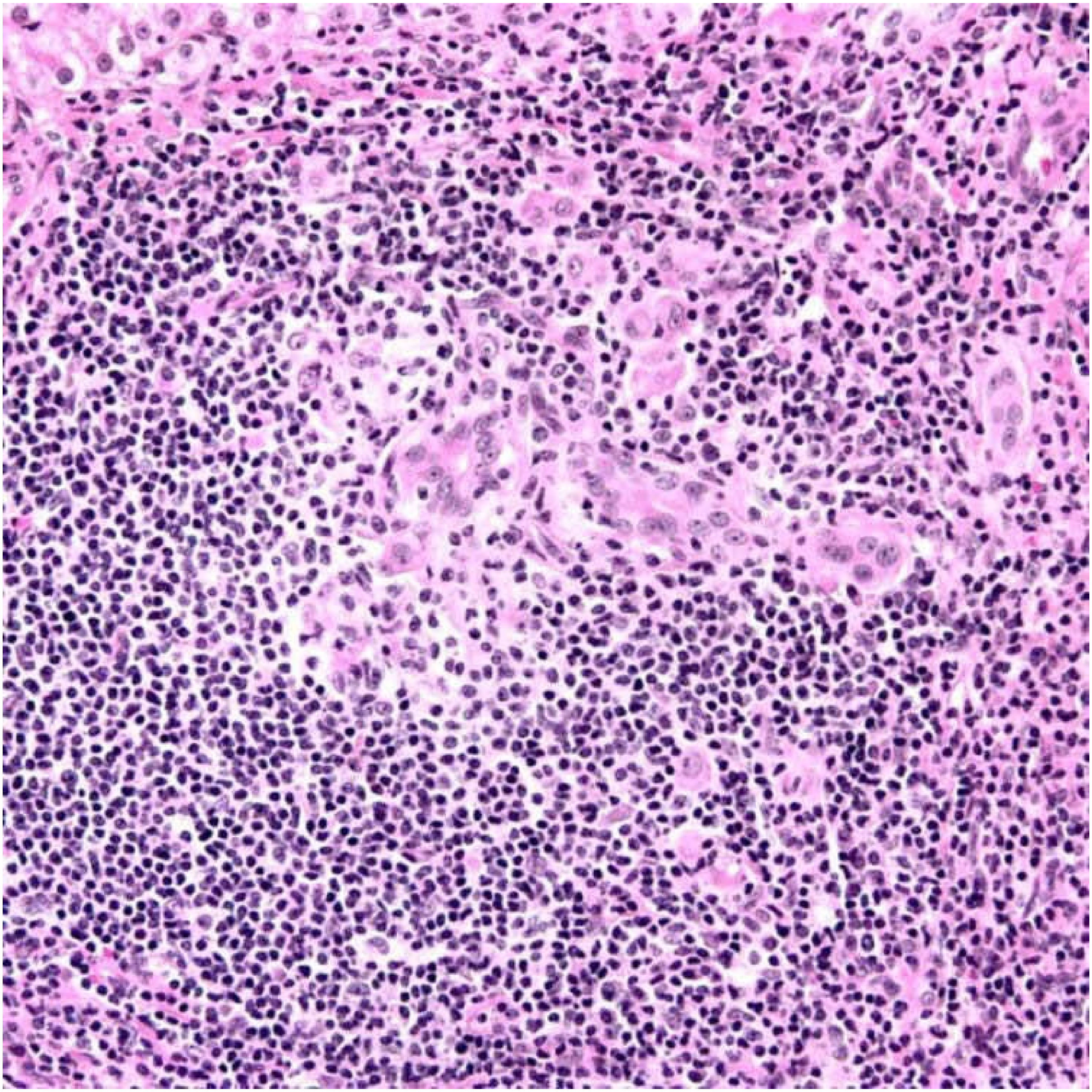
Florid Duct Lesion

This typical florid duct lesion features a granuloma as well as lymphocytic cholangitis and duct epithelial damage, which is characterized by nuclear disarray and cytoplasmic vacuolization.

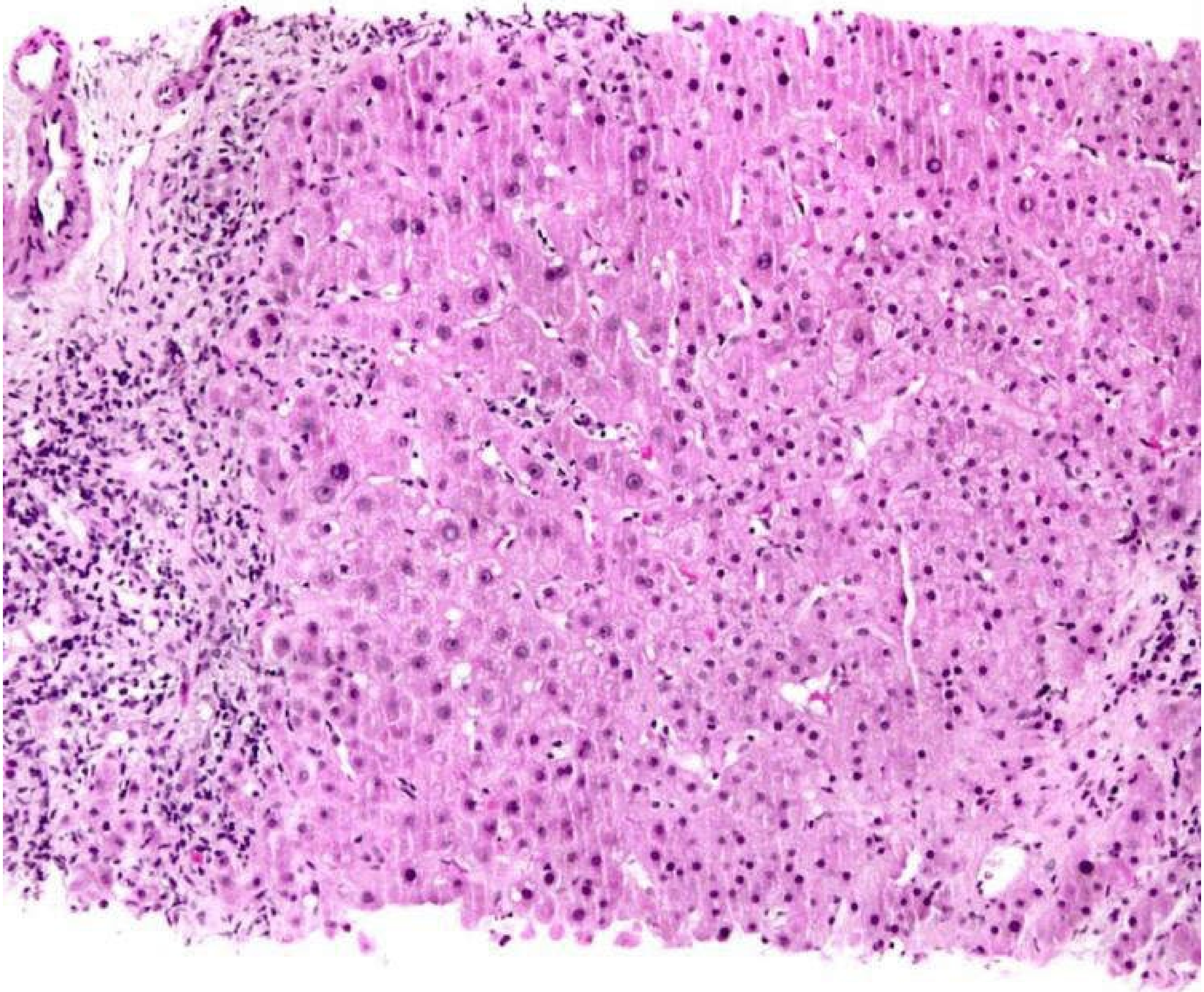


Portal Granuloma

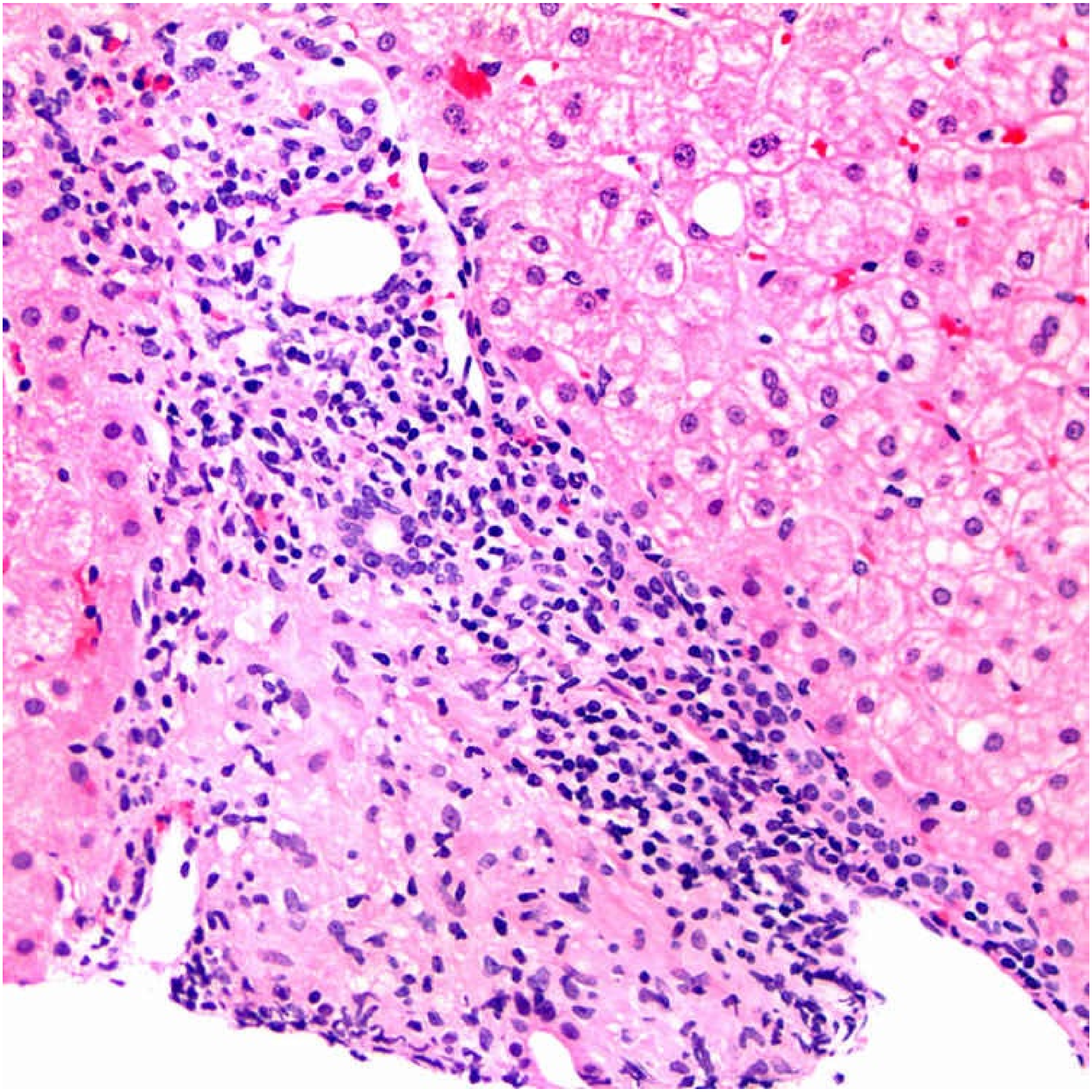
This case of PBC shows a granuloma with giant cells centered on a bile duct with associated portal inflammation and ductular reaction. There is a background of fatty liver. Stage 2 PBC features ductular reaction &/or periportal hepatitis depending on the staging system used.



Lymphocytic Cholangitis
This high-power view of lymphocytic cholangitis shows infiltration of the interlobular bile duct by lymphocytes along with nuclear disarray of the bile duct epithelium. Note the dense surrounding lymphoplasmacytic infiltrate.

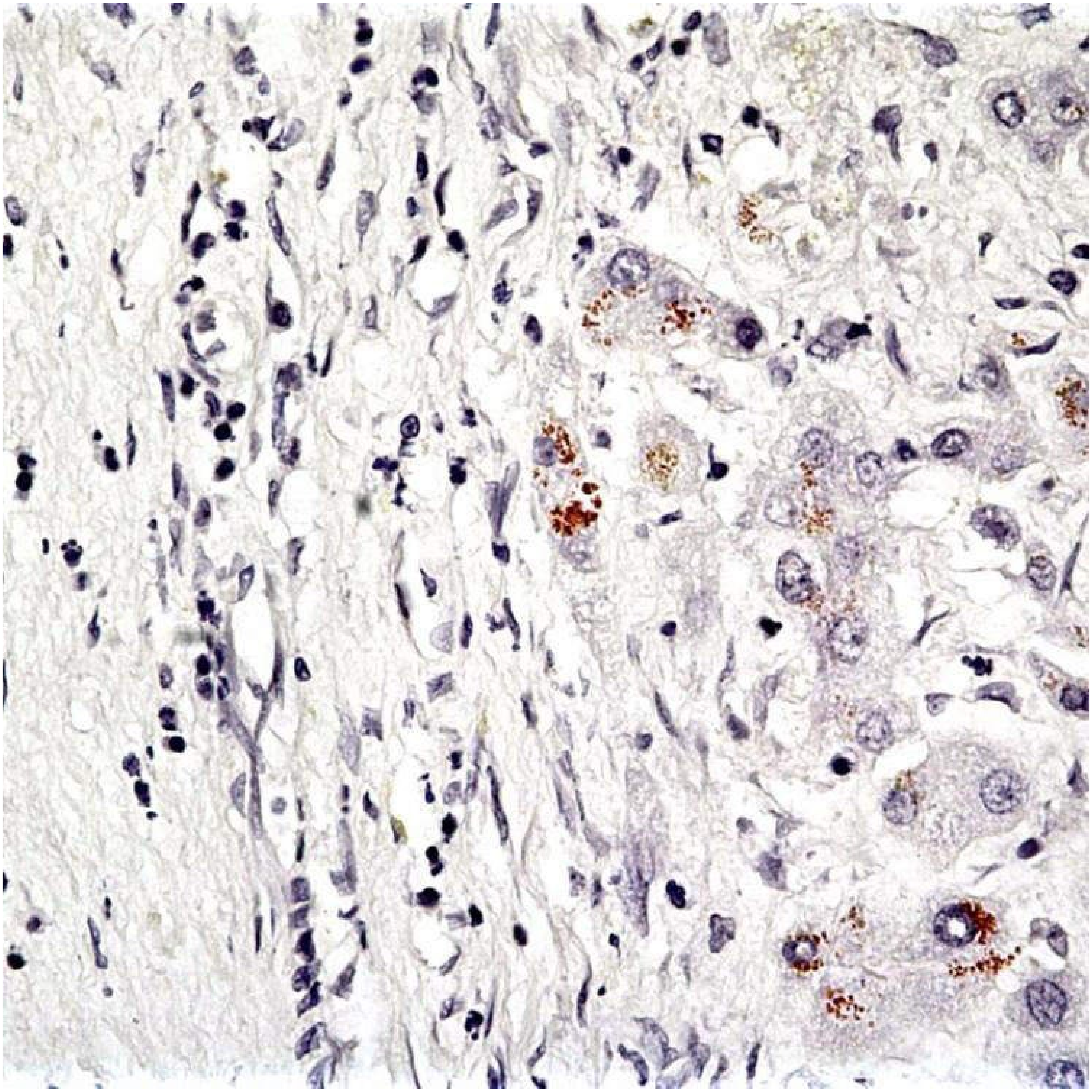


Minimal Lobular Inflammation
PBC usually has only minimal to mild lobular inflammation. If significant lobular activity is seen, autoimmune hepatitis overlap syndrome should be considered. Some PBC cases also have more chronic hepatitis-like portal inflammation, which may lead to diagnostic confusion.

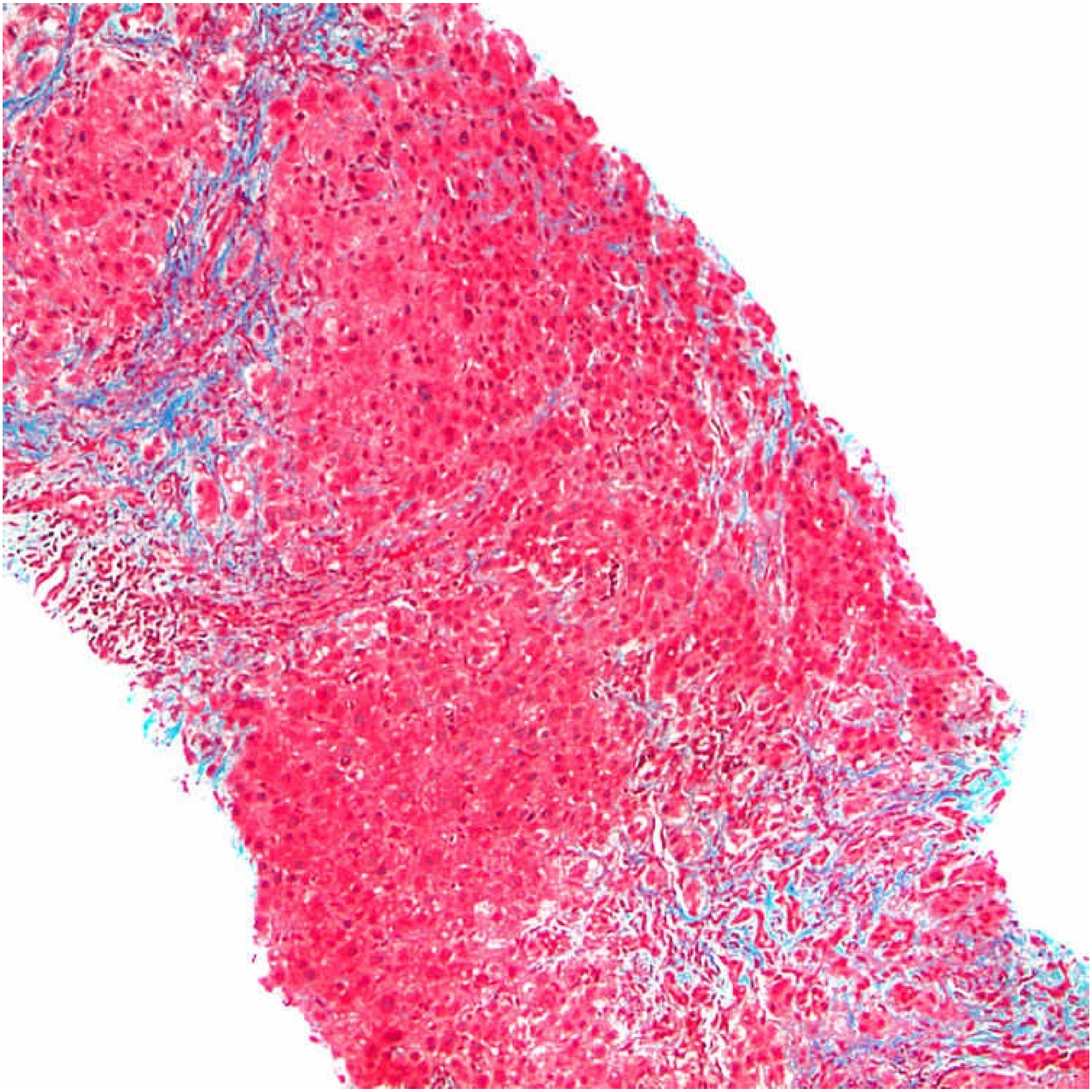


Stage 1

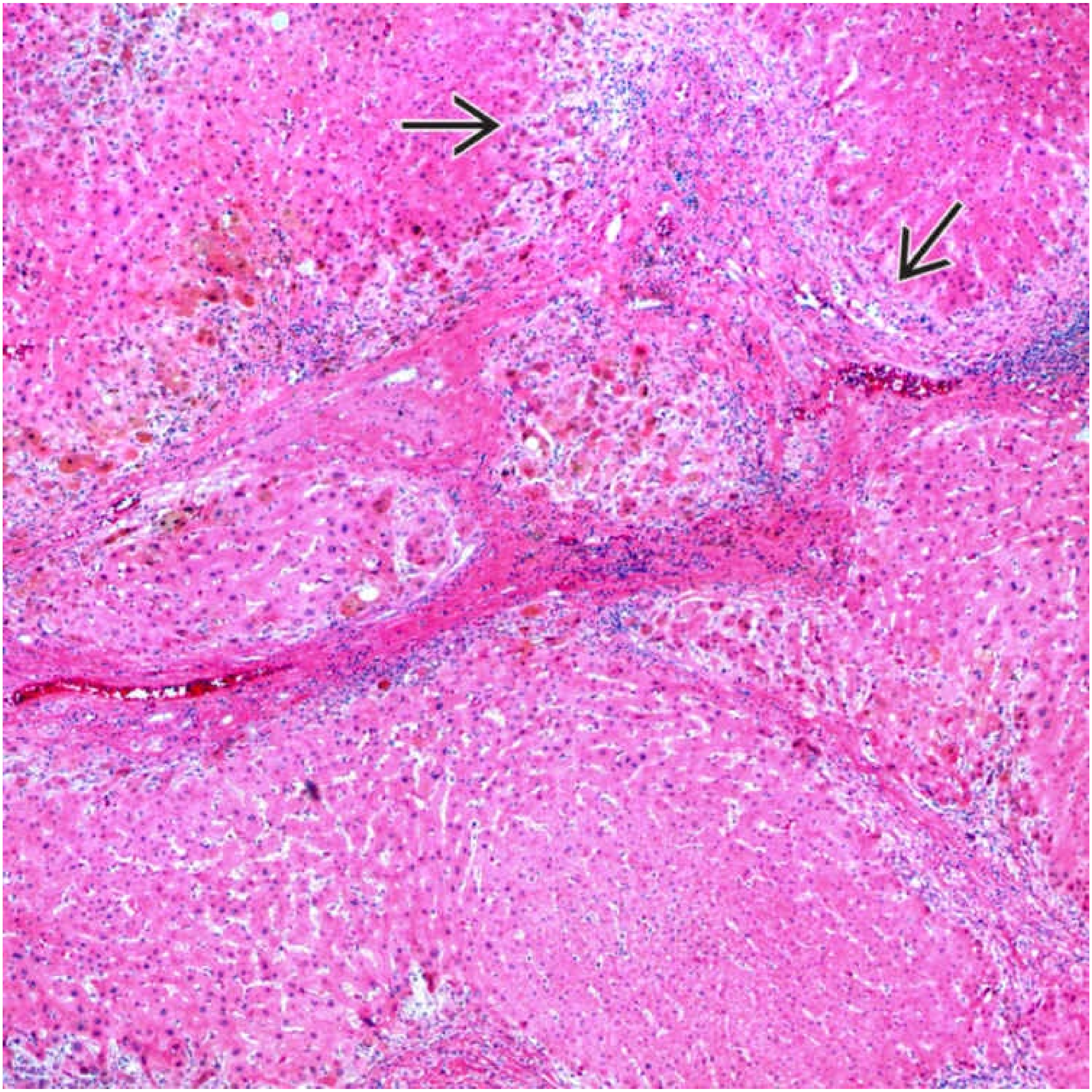
Early (stage 1) PBC is characterized by florid duct lesions and portal inflammation. Note the large epithelioid granuloma. Eosinophils are also present, which are frequently seen in PBC.



Copper Stain
Periportal copper deposition, indicative of chronic cholestasis, is typical of PBC.

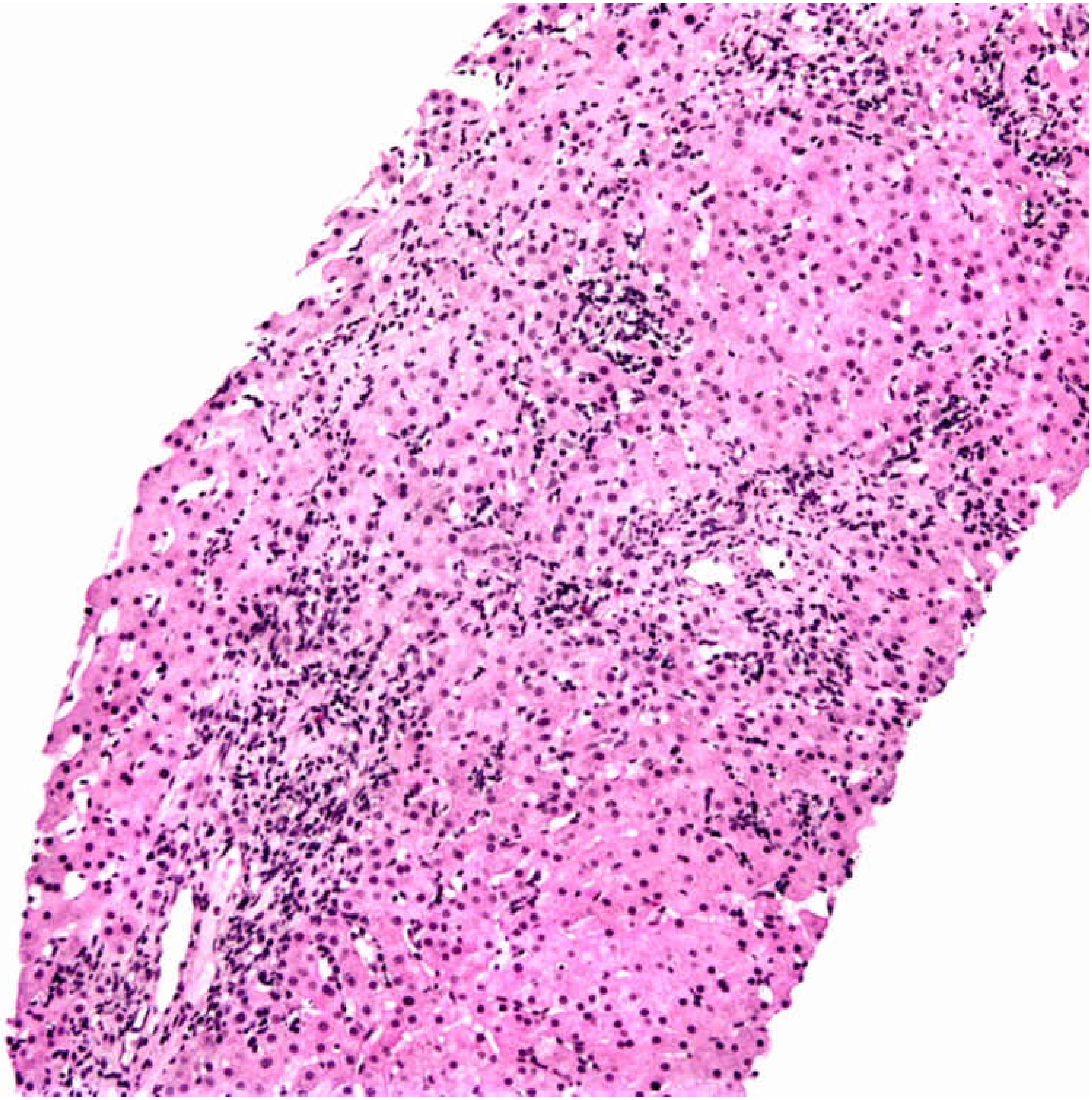


Bridging Fibrosis
Stage 3 PBC is characterized by portal tracts expanded by fibrosis, which then progresses to form portal/portal bridges.

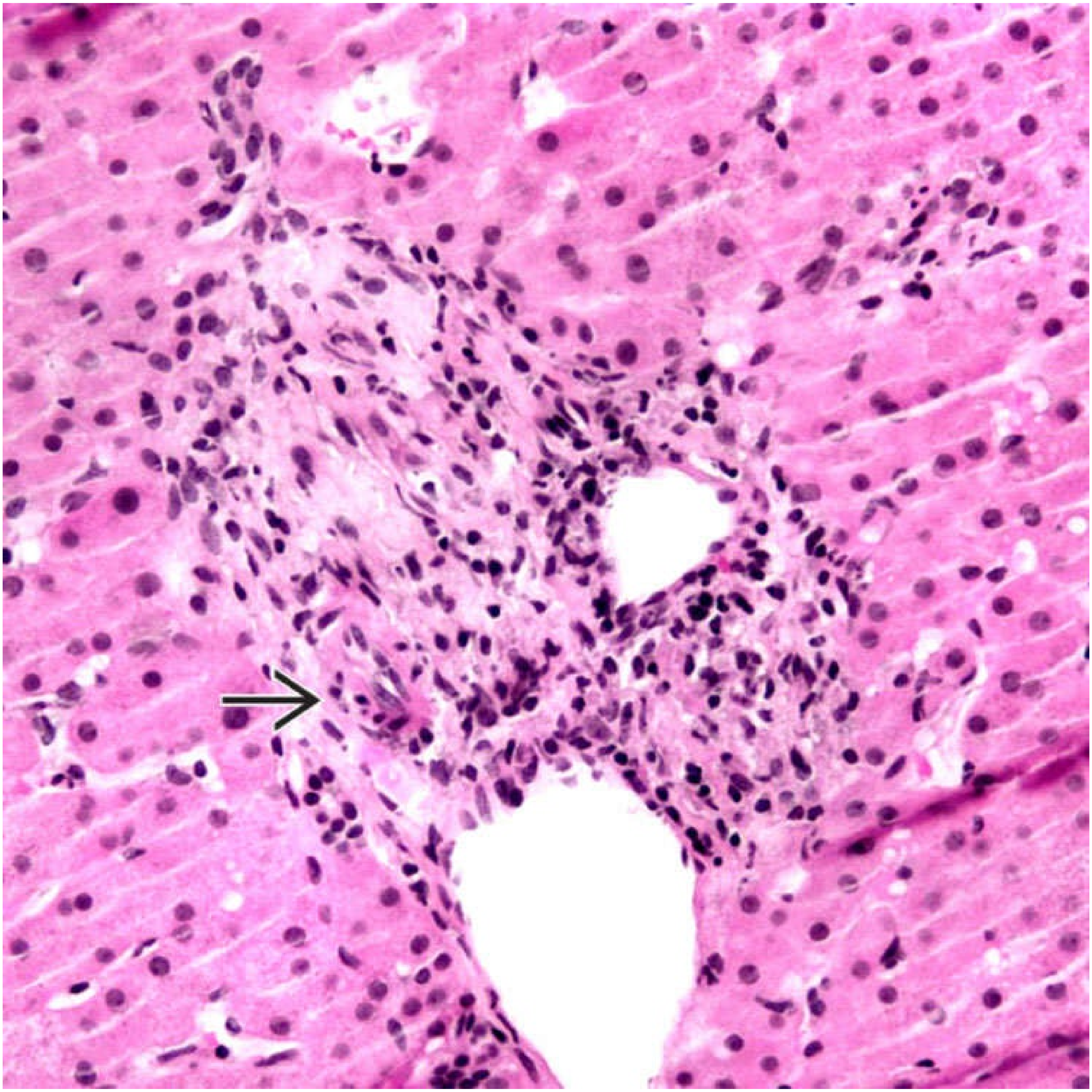


Biliary Cirrhosis

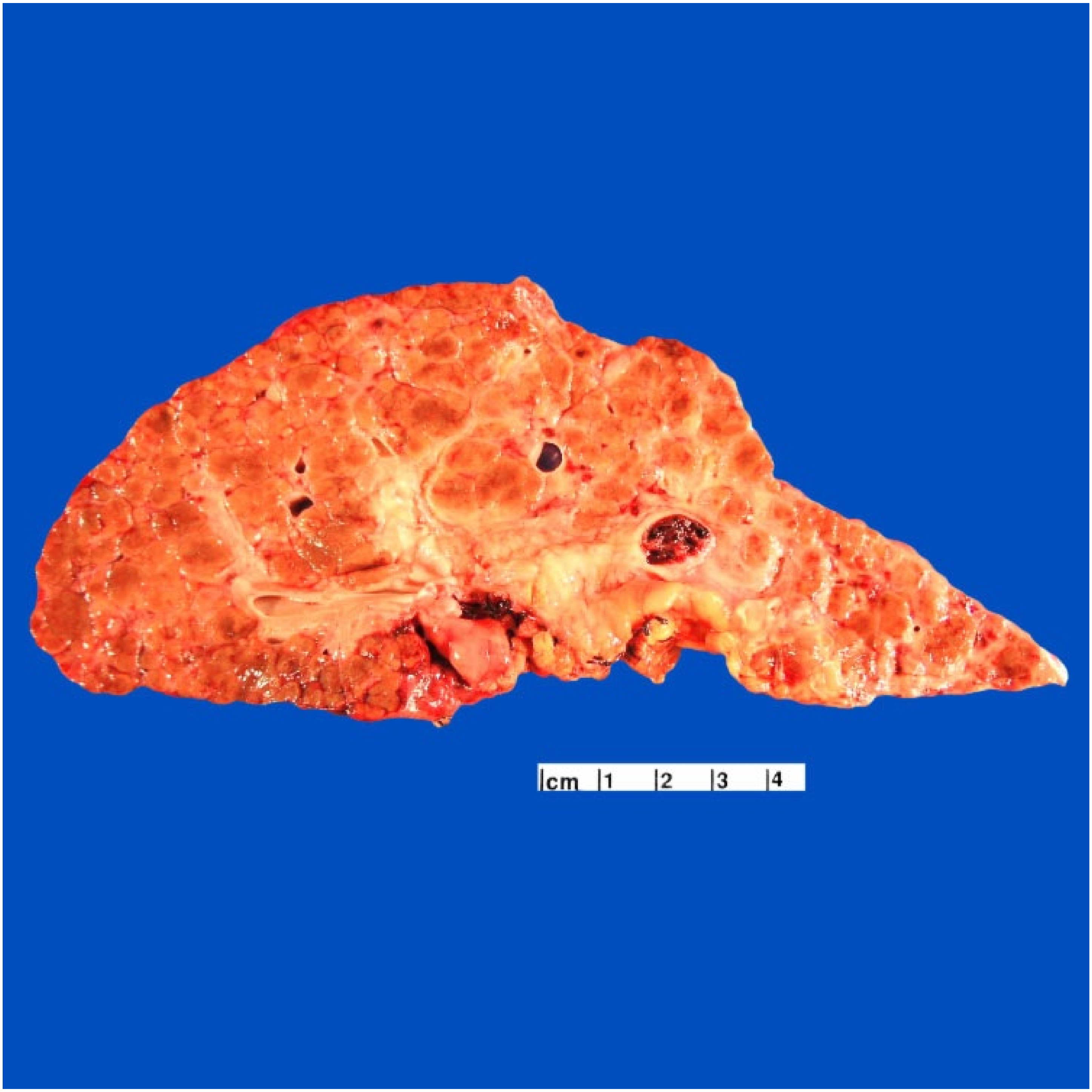
Cirrhosis (stage 4) in PBC is termed biliary-type cirrhosis and features variably sized irregular cirrhotic nodules that are sometimes referred to as jigsaw puzzle pattern fibrosis. Note the “halo” → of swollen hepatocytes and ductular reaction at the edges of the nodules.



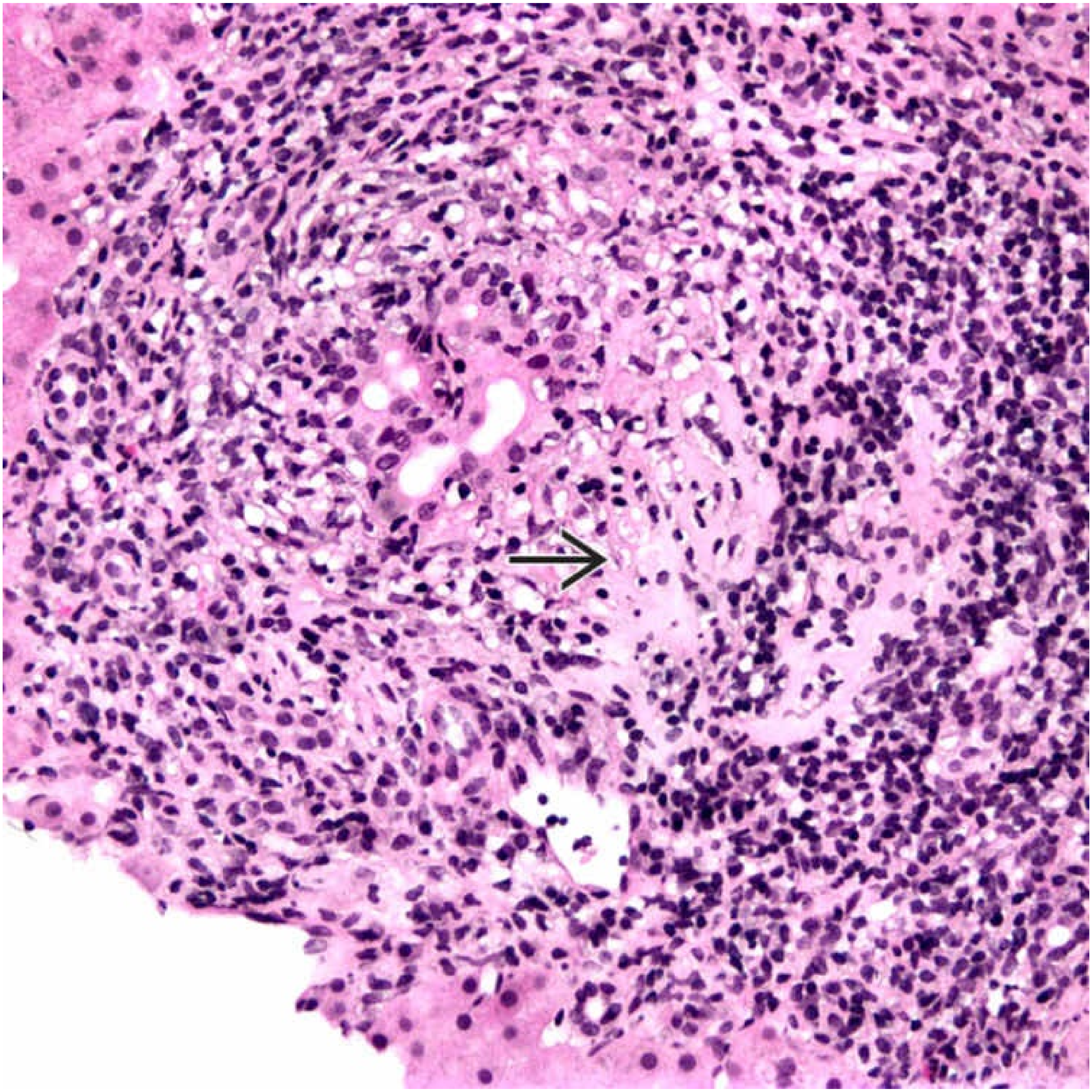
Primary Biliary Cirrhosis/Cholangitis Autoimmune Hepatitis Overlap
In addition to florid duct lesions characteristic of PBC, interface hepatitis and marked lobular hepatitis are seen in this biopsy of PBC-autoimmune hepatitis overlap syndrome.



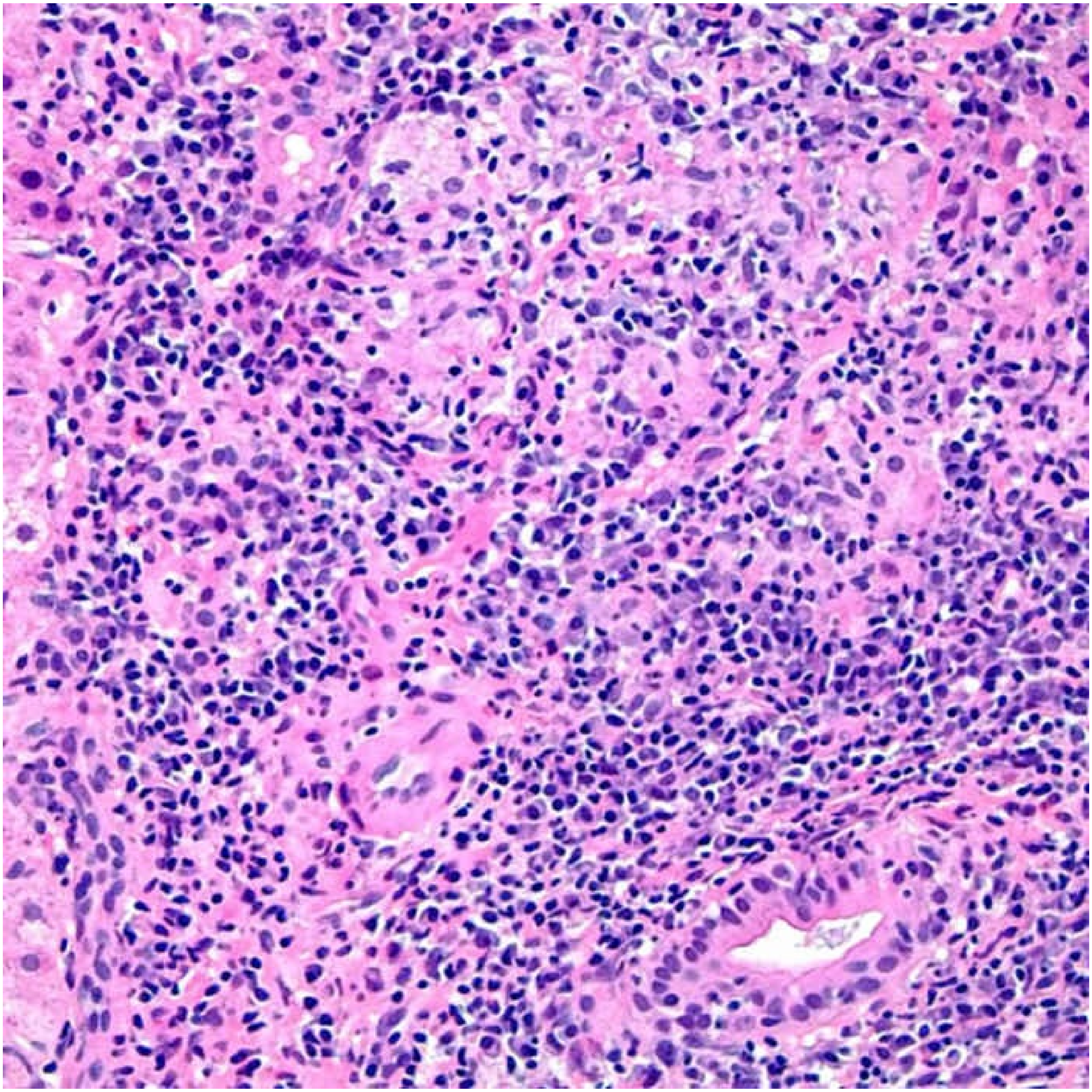
Primary Biliary Cirrhosis/Cholangitis Autoimmune Hepatitis Overlap, Duct Loss
This case of PBC-autoimmune hepatitis overlap syndrome shows loss of the interlobular bile duct in the portal tract with mild inflammation. The presence of the hepatic arteriole → without an accompanying duct is indicative of duct loss.



This explanted liver is from a patient with. Note the nodular cut surface and the green color, indicating chronic cholestasis.



A high-power view of PBC-autoimmune hepatitis overlap syndrome features a florid duct lesion with granulomatous inflammation → and marked interface hepatitis.



Hematoxylin and eosin of autoimmune cholangitis [AMA(-) PBC] illustrates a florid duct lesion with inflammatory cell infiltrate and abundant plasma cells.

SELECTED REFERENCES

1. Flores, A, et al. Primary biliary cirrhosis in 2014. *Curr Opin Gastroenterol*. 2014; 30(3):245–252.
2. Washington, MK. Autoimmune liver disease: overlap and outliers. *Mod Pathol*. 2007; 20(Suppl 1):S15–S30.
3. Kaplan, MM, et al. Primary biliary cirrhosis. *N Engl J Med*. 2005 Sep 22; 353(12):1261–1273. [Review. Erratum in: N Engl J Med. 354(3):313, 2006].
4. Chazouillères, O, et al. Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome: clinical features and response to therapy. *Hepatology*. 1998; 28(2):296–301.
5. Taylor, SL, et al. Primary autoimmune cholangitis. An alternative to antimitochondrial antibody-negative primary biliary cirrhosis. *Am J Surg Pathol*. 1994; 18(1):91–99.

Primary Sclerosing Cholangitis

KEY FACTS

Terminology

- Chronic cholestatic disease featuring progressive inflammation and fibrosis of intrahepatic and extrahepatic biliary tree
  - May affect large bile ducts (both intra- and extrahepatic), small bile ducts, or both

Etiology/Pathogenesis

- Unknown etiology
  - Frequent association with inflammatory bowel disease, particularly ulcerative colitis

Clinical Issues

- Predilection for young and middle-aged men
  - Majority of patients are asymptomatic at diagnosis
  - Elevated alkaline phosphatase in over 90% of patients
  - Progresses to biliary cirrhosis in majority of patients within 10-15 years
  - Essentially no effective medical therapy
  - Liver transplantation for end-stage liver disease
- Increased risk of cholangiocarcinoma, colorectal carcinoma, and gallbladder carcinoma

Imaging

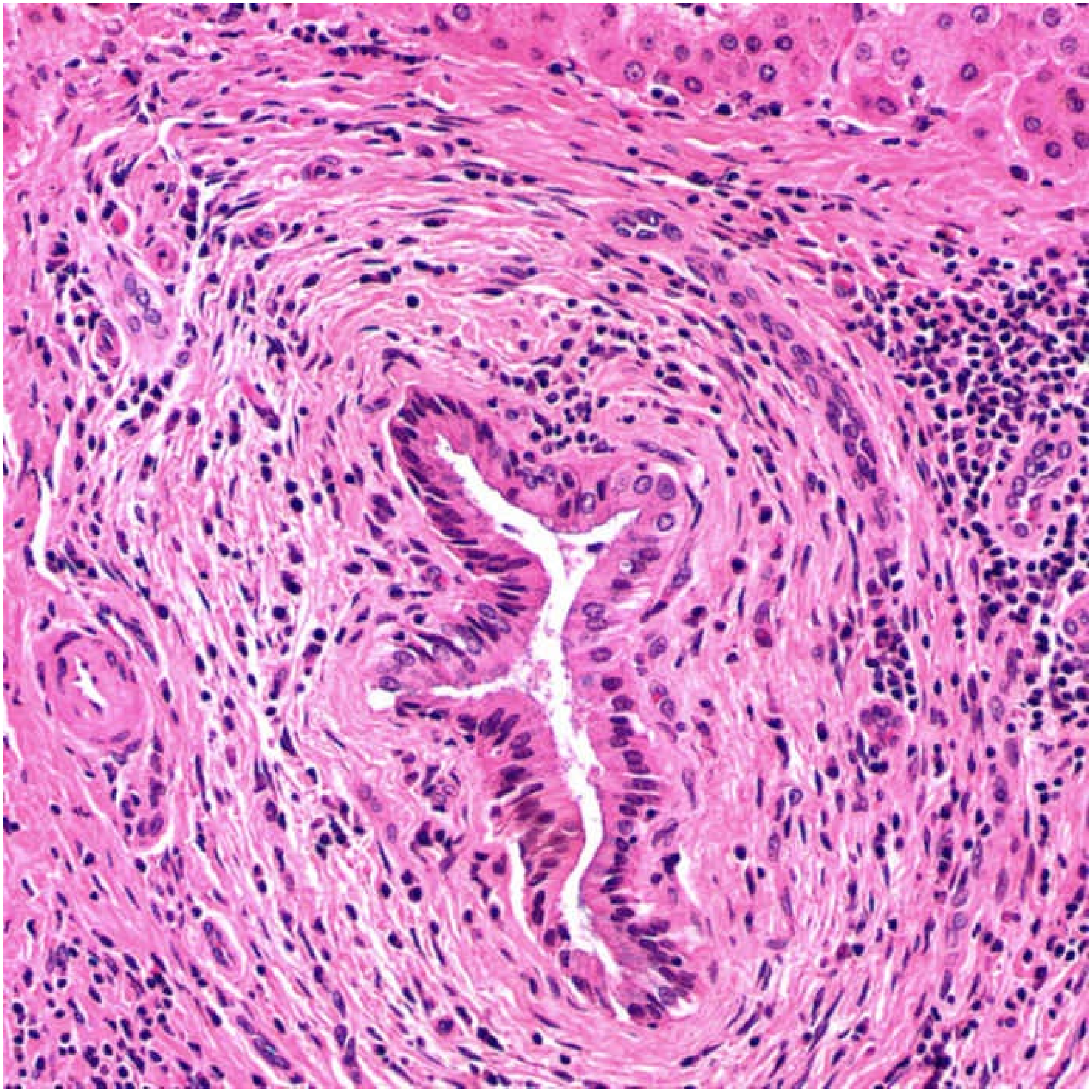
- Cholangiography is diagnostic gold standard
  - Characteristic beaded appearance of biliary tree secondary to segmental strictures

Microscopic

- Findings often patchy and nonspecific, making biopsy diagnosis difficult
  - Concentric fibrosis around affected bile ducts with onion skin appearance
    - Present only in minority of biopsy samples
- Lymphocytic cholangitis

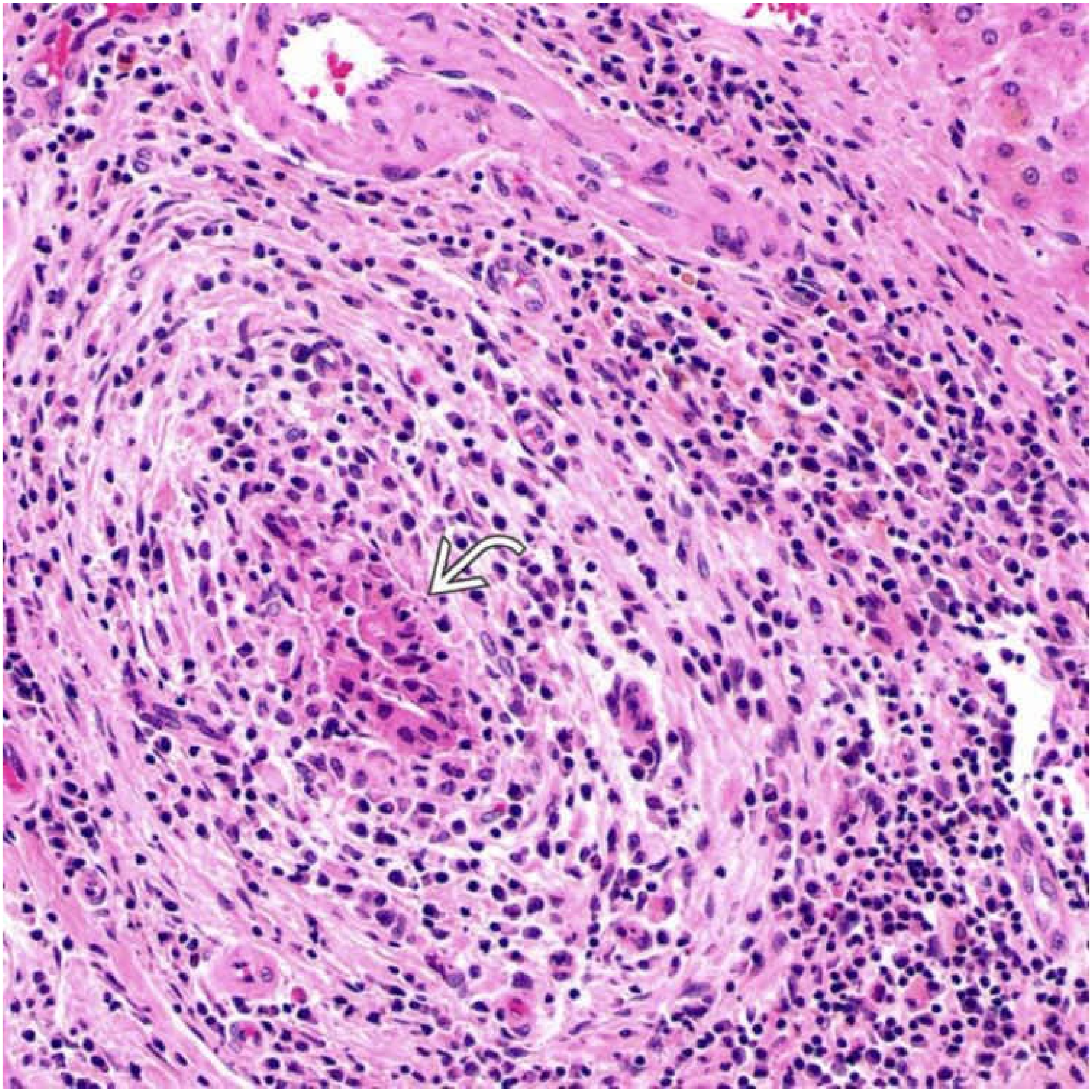
• Degeneration and atrophy of duct epithelium
  ○ Eventual obliteration of ducts with variable scarring
• Periportal copper deposition indicates chronic cholestasis

ERCP
A classic ERCP of primary sclerosing cholangitis (PSC) shows multiple segmental strictures of the biliary tree, resulting in a beaded appearance ⇨. There are also diverticular outpouchings of dilated bile ducts ⇨.

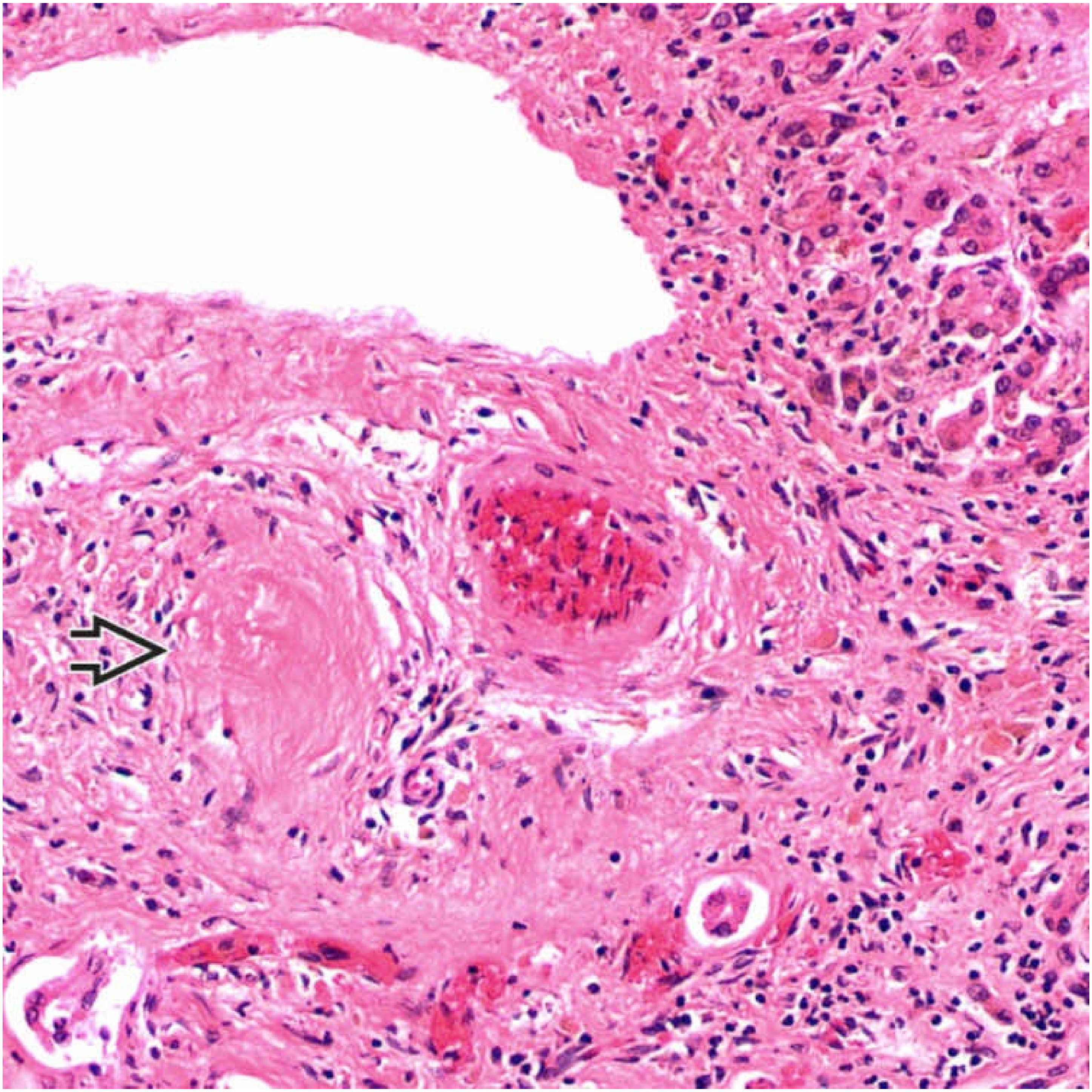


Onion Skin Lesion

The classic onion skin lesion of PSC consists of concentric fibrosis around a bile duct. There is mild lymphoplasmacytic infiltration of the portal tract and lymphocytic cholangitis in the duct epithelium.



Inflammation and Duct Damage
This case of PSC shows markedly damaged duct epithelium, as well as lymphoplasmacytic infiltration of the duct, periductal stroma, and portal tract. Lymphocytic cholangitis is apparent within the remaining ductal epithelium .



Duct Loss With Scar
This interlobular bile duct has been entirely replaced by a round fibroobliterative scar ➪. The hepatic artery and portal vein branches are unremarkable.

TERMINOLOGY

Abbreviations

• Primary sclerosing cholangitis (PSC)

Definitions

• Chronic cholestatic disease featuring progressive inflammation and fibrosis of intrahepatic and

extrahepatic biliary tree

ETIOLOGY/PATHOGENESIS

Unknown

- Frequent association with HLA-B8 and DR3
  - 100x increased risk of disease in 1st-degree relatives of patients with PSC
- Associated with chronic idiopathic inflammatory bowel disease (IBD), particularly ulcerative colitis
  - ~ 70% of patients with PSC have ulcerative colitis
  - 2.0-7.5% of patients with ulcerative colitis have PSC
  - 1.4-3.4% of patients with Crohn disease have PSC
- May affect large bile ducts (both intra- and extrahepatic), small bile ducts, or both

CLINICAL ISSUES

Epidemiology

- Incidence
  - ~ 1 in 100,000 people
  - – Highest in people with Northern European ancestry
- Age
  - Any age, common from 20-50 years
    - – Median: 35-47
- Sex
  - Close to 70% of patients are male

Presentation

- Majority of patients are asymptomatic at diagnosis
  - Diagnosis often results from investigation of abnormal liver tests
- Nonspecific signs/symptoms
  - Fatigue
  - Abdominal pain
  - Pruritus/jaundice
  - Weight loss

Laboratory Tests

- Elevated alkaline phosphatase in > 90% of patients
  - Transaminases may be 2-3x normal limits but may not be elevated
  - Bilirubin typically normal at diagnosis
  - Elevation more common in advanced disease
- Nonspecific antibodies often present including ANA, SMA, ANCA

Treatment

- Essentially no effective medical therapy
  - Use of ursodeoxycholic acid controversial
- Endoscopic balloon dilation or stenting
- Liver transplantation for end-stage liver disease
  - Reportedly recurs in up to 1/2 of transplant recipients within 10 years

Prognosis

- Progresses to biliary cirrhosis in majority of patients within 10-15 years
  - Slightly < 20% of asymptomatic patients have cirrhosis at time of diagnosis
- Increased risk of cholangiocarcinoma
  - 160x higher than general population
  - Risk factors include older age at PSC diagnosis, smoking, alcohol use, longer duration of IBD
  - Surveillance is recommended (imaging and serum CA19-9 level)
    - Effectiveness of surveillance is unclear
- Increased risk of gallbladder carcinoma
  - 2% of patients with PSC
- Increased risk of colorectal adenocarcinoma
  - Higher than in patients with IBD alone
    - Patients who have undergone liver transplant for PSC may have even greater risk than pretransplant
  - Frequent (every 1-2 year) colonoscopy is recommended

IMAGING

Cholangiography (ERCP or MRCP)

- Considered diagnostic gold standard
  - Characteristic beaded appearance of intrahepatic and extrahepatic biliary tree, attributed to alternating segmental strictures and saccular dilations of affected bile ducts
- Virtually diagnostic except for small duct variant

MACROSCOPIC

General Features

- Cirrhotic livers are nodular and green and show annular scarring and saccular dilatation of large ducts

MICROSCOPIC

Histologic Features

- Inflammation and fibrosis of bile ducts

- Concentric fibrosis around bile ducts with onion skin appearance
  - Rare finding on biopsy specimen
  - Many damaged ducts lack associated fibrosis
- Degeneration and damage to duct epithelium
  - Cytoplasmic vacuolization, nuclear disarray
  - Progressive duct atrophy and loss
  - Eventual obliteration of duct may leave round fibroobliterative scar
    - Many obliterated ducts do not have scar but are simply absent
    - Can gauge by noting presence of hepatic artery branches that lack accompanying bile duct
- Lymphocytic infiltration of bile ducts
- Ductular reaction
- Periportal copper deposition indicates chronic cholestasis
- Portal inflammation
  - Typically minimal to mild
  - Predominantly lymphocytic with occasional small lymphoid aggregates
    - Variably present admixed portal eosinophils and plasma cells

- Progressive portal expansion leads to bridging fibrosis and biliary cirrhosis
  - Highly irregular, geographic or jigsaw puzzle nodular pattern
  - Ductopenia
    - Ductular reaction may become more prominent
  - Cholate stasis (periseptal hepatocyte swelling, Mallory hyaline, copper deposition)
- Variants
  - Small duct PSC
    - Pure form seen in ~ 5% of PSC patients
    - Lacks characteristic ERCP findings, thus diagnosis based on biopsy
    - More frequently associated with Crohn disease
    - More favorable outcome, although 25% progress to large-duct disease
  - Overlap syndrome
    - Overlap with autoimmune hepatitis in 1.4-8.0% of patients with PSC
      - More common in pediatric patients (up to 49%)
    - Has additional clinical, laboratory, and histologic features of autoimmune hepatitis
    - Immunosuppressive therapy is beneficial
- Staging
  - 1: Portal
    - Portal inflammation and bile duct abnormalities
  - 2: Periportal
    - Periportal fibrosis, fibrous expansion of portal tract
  - 3: Septal (bridging)
    - Fibrous septa

- 4: Cirrhosis

DIFFERENTIAL DIAGNOSIS

Large Bile Duct Obstruction

- Portal edema, ductular reaction, portal neutrophils, and cholestasis are more prominent
- Usually lacks signs of chronic cholestatic disease, such as duct loss and copper deposition
- Usually portal tracts are more uniformly involved
- Rapid development of fibrosis if left untreated

IgG4-Associated Cholangitis

- Associated with other IgG4-related fibrosclerosing diseases (such as autoimmune pancreatitis); no association with IBD
- Primarily involves extrahepatic bile ducts
- Numerous IgG4(+) plasma cells

Ischemic Cholangiopathy

- Impaired blood supply to biliary tree due to surgery or hepatic artery thrombosis

Infectious Cholangitis

- HIV, CMV, coccidians, etc.

Primary Biliary Cholangitis

- Typically female patients with positive AMA
- Lacks granuloma and dense portal lymphoplasmacytic infiltrates
- Lacks typical cholangiographic findings

Drug-Induced Injury

- Numerous antibiotics, Haldol, amitriptyline, some antihypertensives, etc.

Chronic Hepatitis C

- Lacks significant bile duct damage, duct loss, and copper deposition
- Distinction may require correlation with laboratory, imaging, and clinical information

Chronic Allograft Rejection

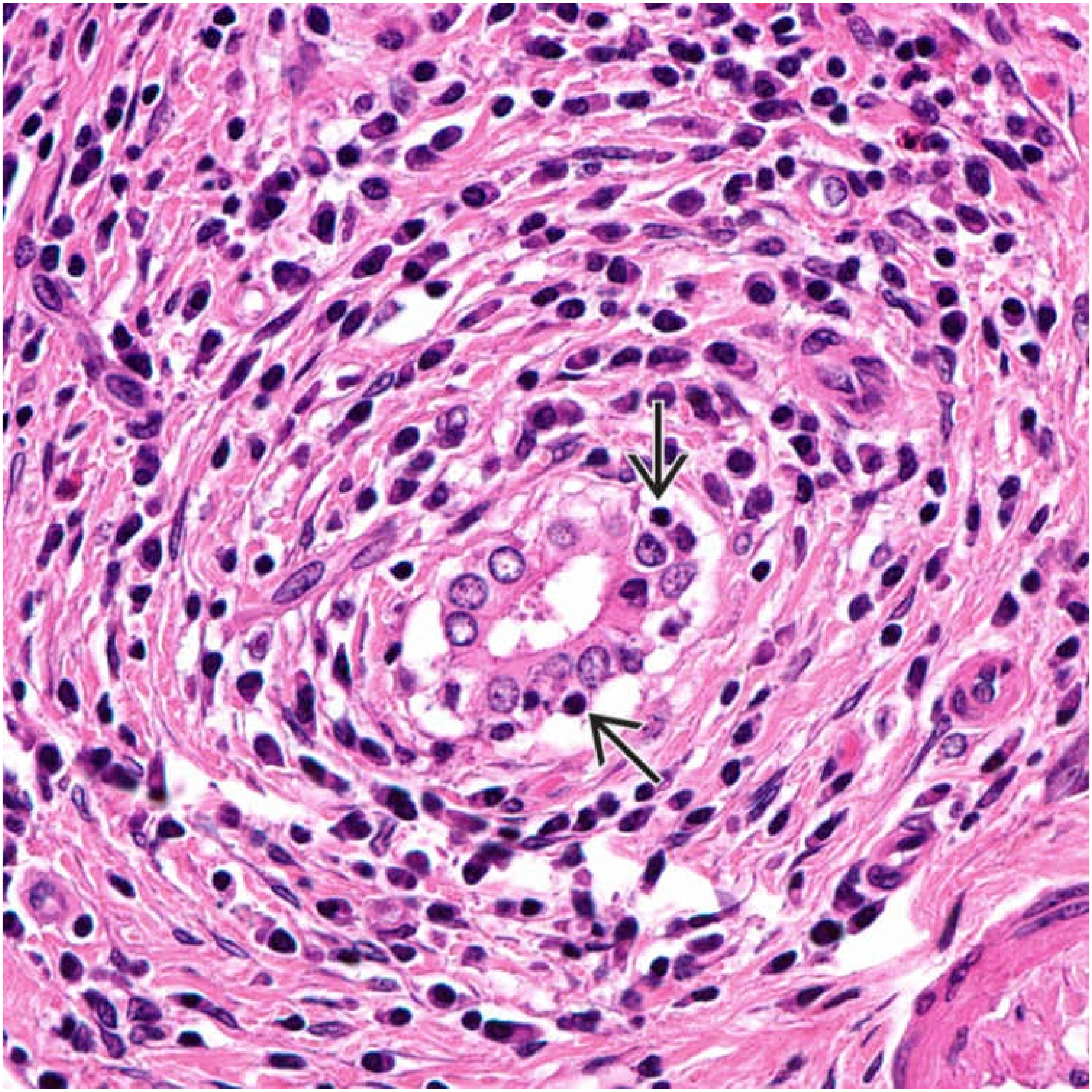
- Ductopenia is typically not accompanied by fibroobliterative scar, progressive fibrosis, ductular reaction, and copper deposition
- Usually preceded by episodes of acute rejection

- Central perivenulitis may be seen

DIAGNOSTIC CHECKLIST

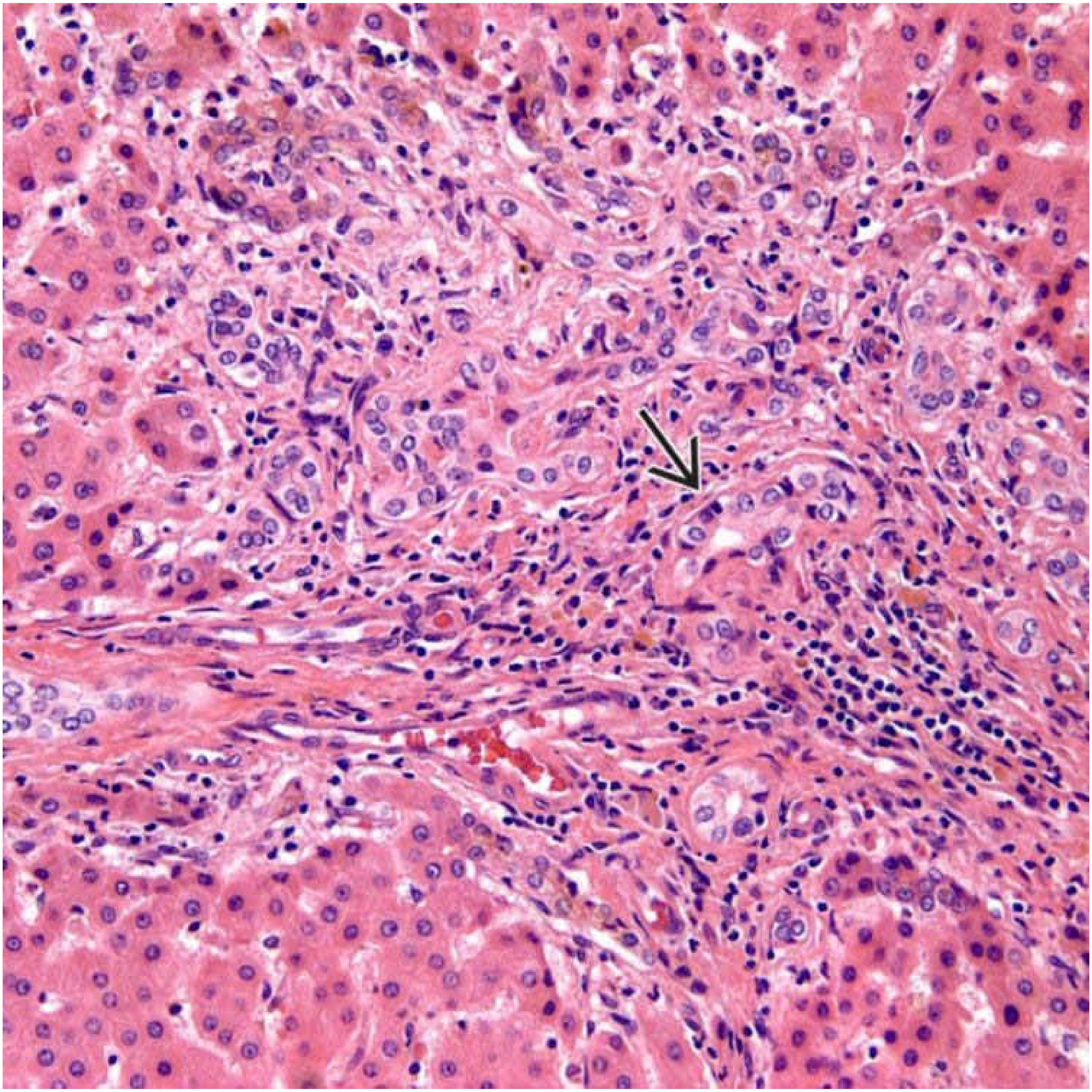
Pathologic Interpretation Pearls

- Diagnostic features may not be evident in needle biopsy due to patchy nature of disease
- Histologic features are very heterogeneous, and many are not specific or diagnostic of PSC
- Carefully look for features of PSC in liver biopsies of patients with IBD, especially if liver tests are cholestatic



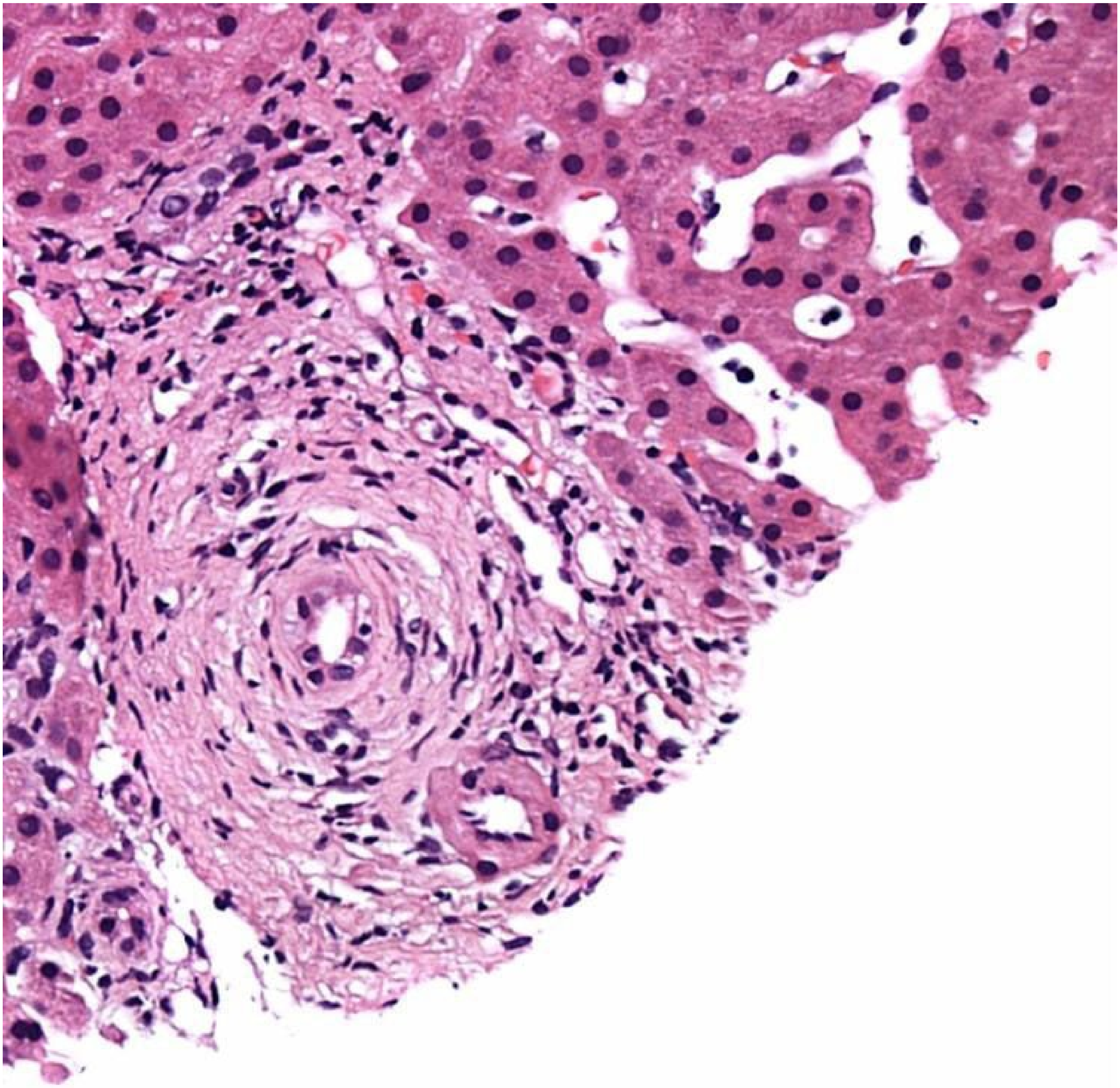
Lymphocytic Cholangitis

This case of PSC shows typical findings, including lymphocytic cholangitis → and degenerative changes of the duct epithelium, including cytoplasmic vacuolation and nuclear disarray. Portal lymphoplasmacytic infiltrates and periductal laminar collagen deposition are evident.

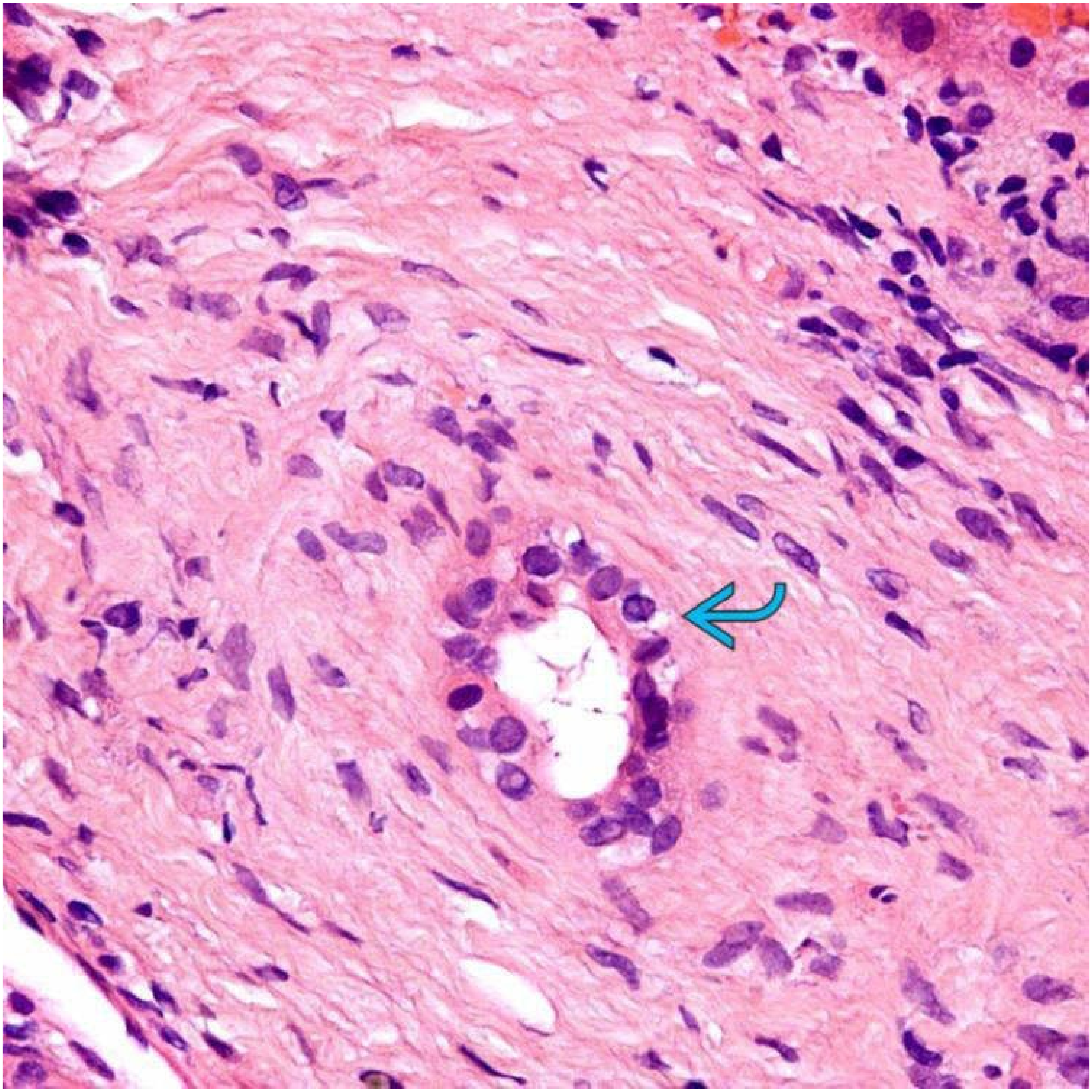


Ductular Reaction

This portal tract shows marked ductular reaction. The interlobular bile ducts contain infiltrating lymphocytes →. There is mild portal inflammation as well.



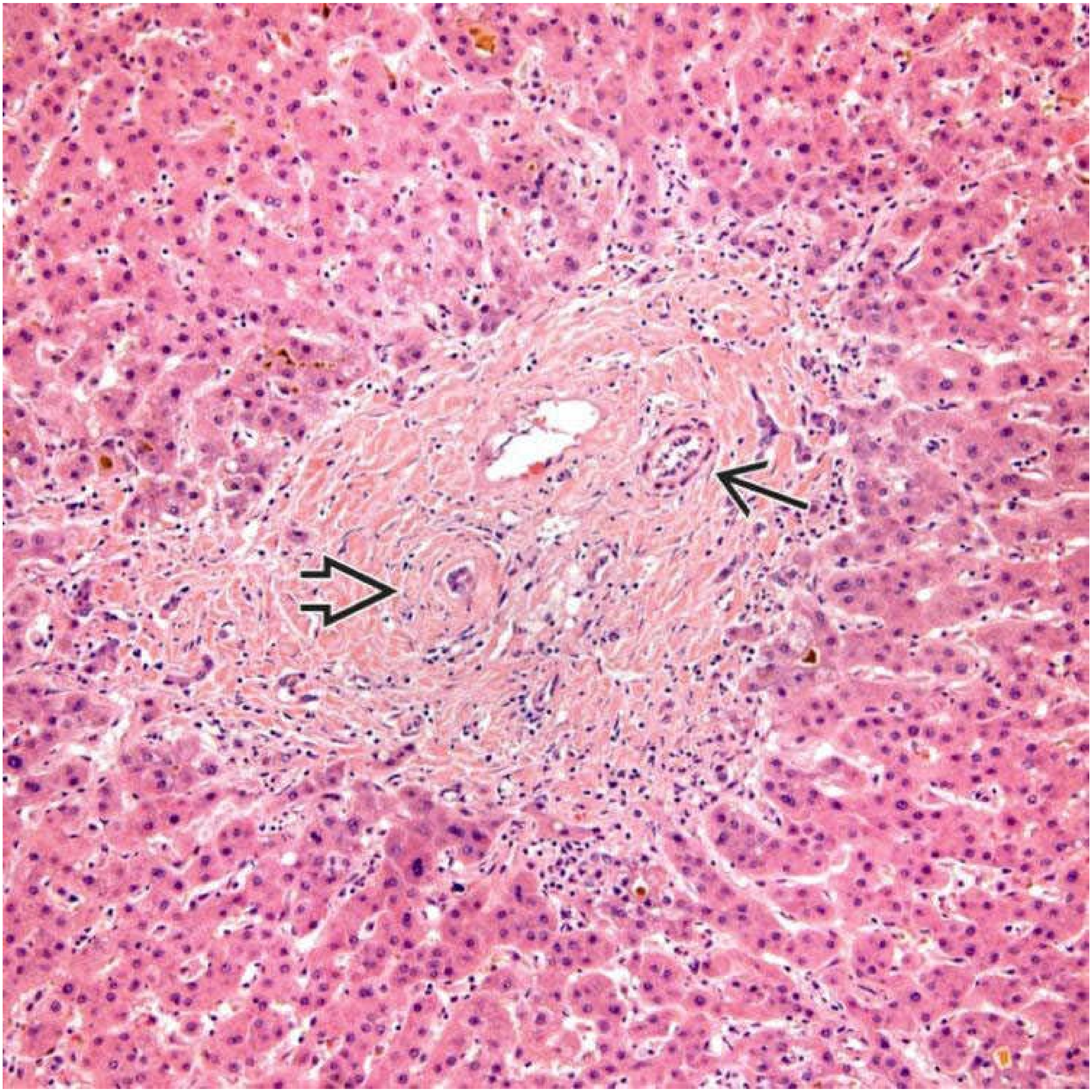
Duct Injury
This portal tract contains an atrophic interlobular bile duct with cytoplasmic vacuolization and marked nuclear disarray. There is periductal fibrosis as well as mild lymphoplasmacytic inflammation.



Epithelial Damage

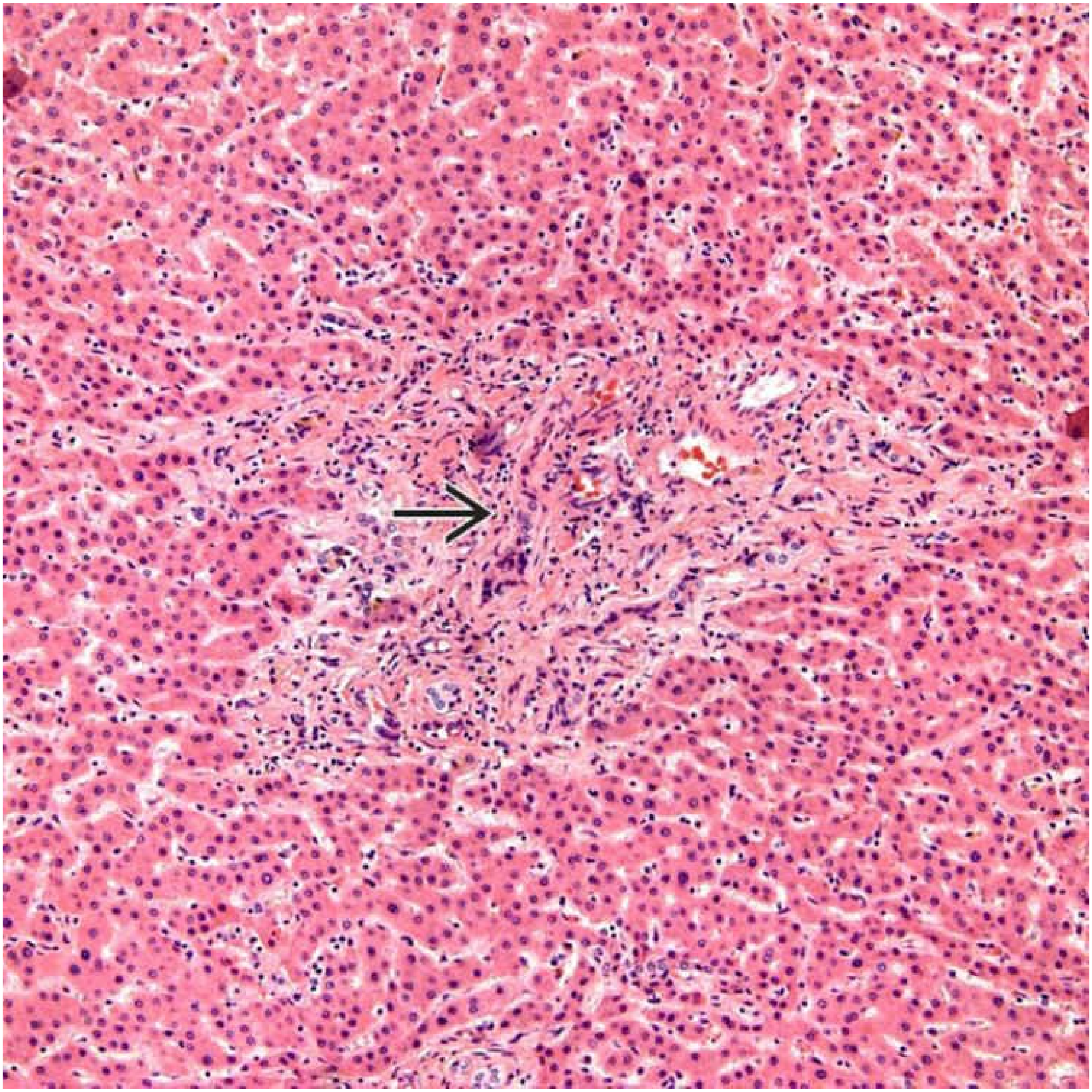
This high-power photograph of a damaged duct shows nuclear disarray and cytoplasmic vacuolization.

Note the surrounding periductal fibrosis.

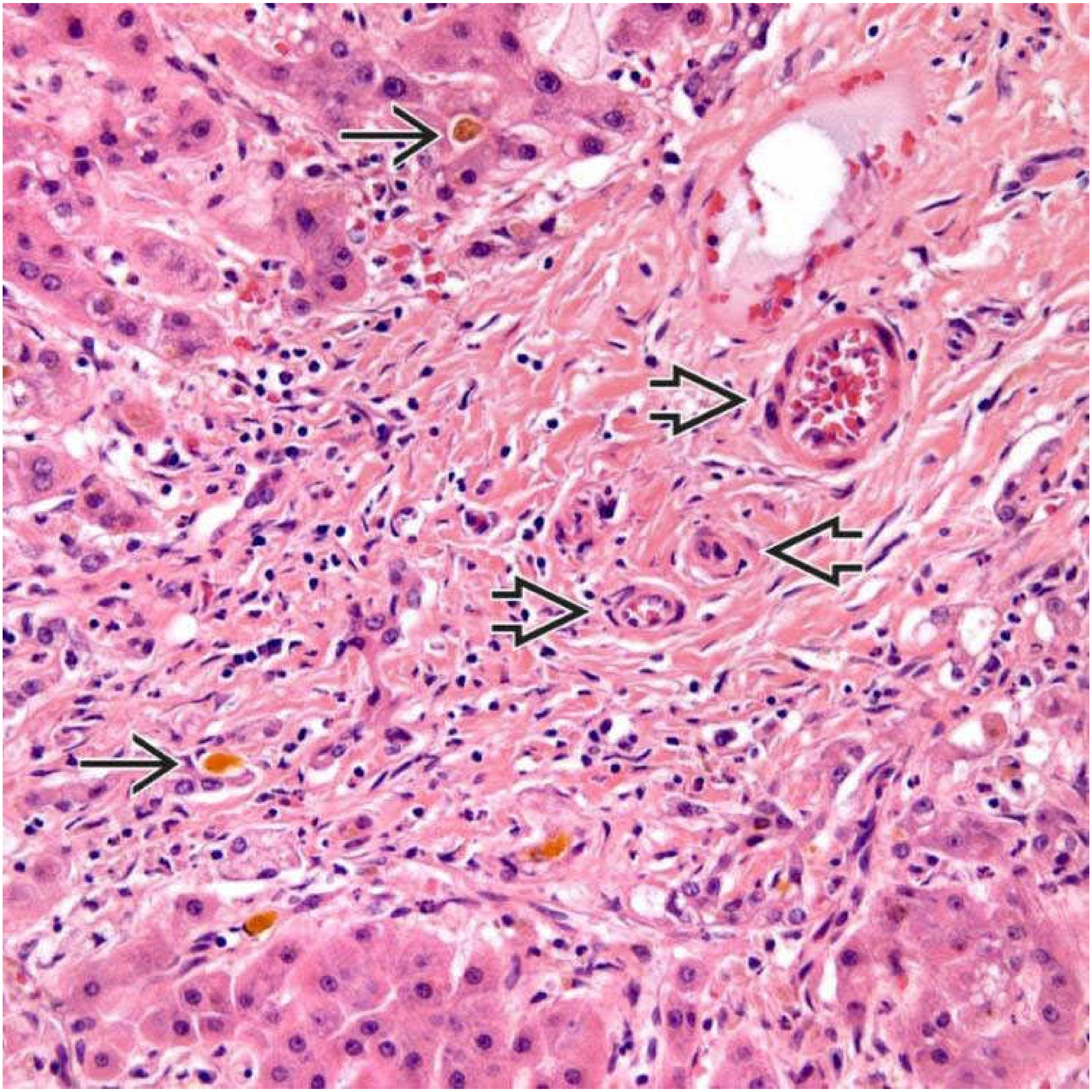


Duct Atrophy

This irregular, expanded portal tract shows a hepatic arteriole → and an adjacent interlobular bile duct with marked atrophy ⇨. There is minimal inflammation, cholestasis, and mild ductular reaction.

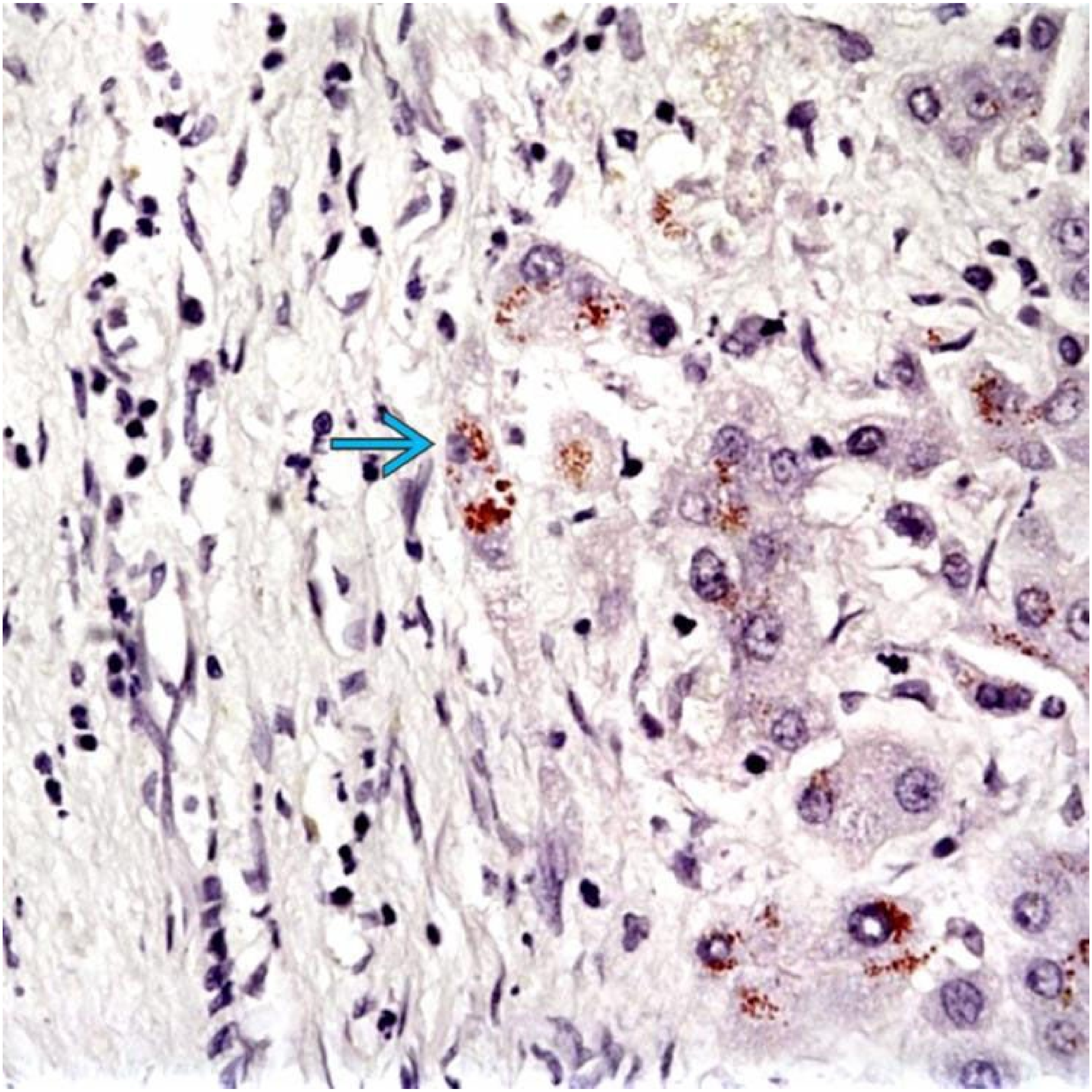


Portal Expansion and Duct Atrophy
This portal tract shows mild fibrotic expansion with irregular contours. The interlobular bile duct appears atrophic →. There is mild ductular reaction and only minimal inflammation.

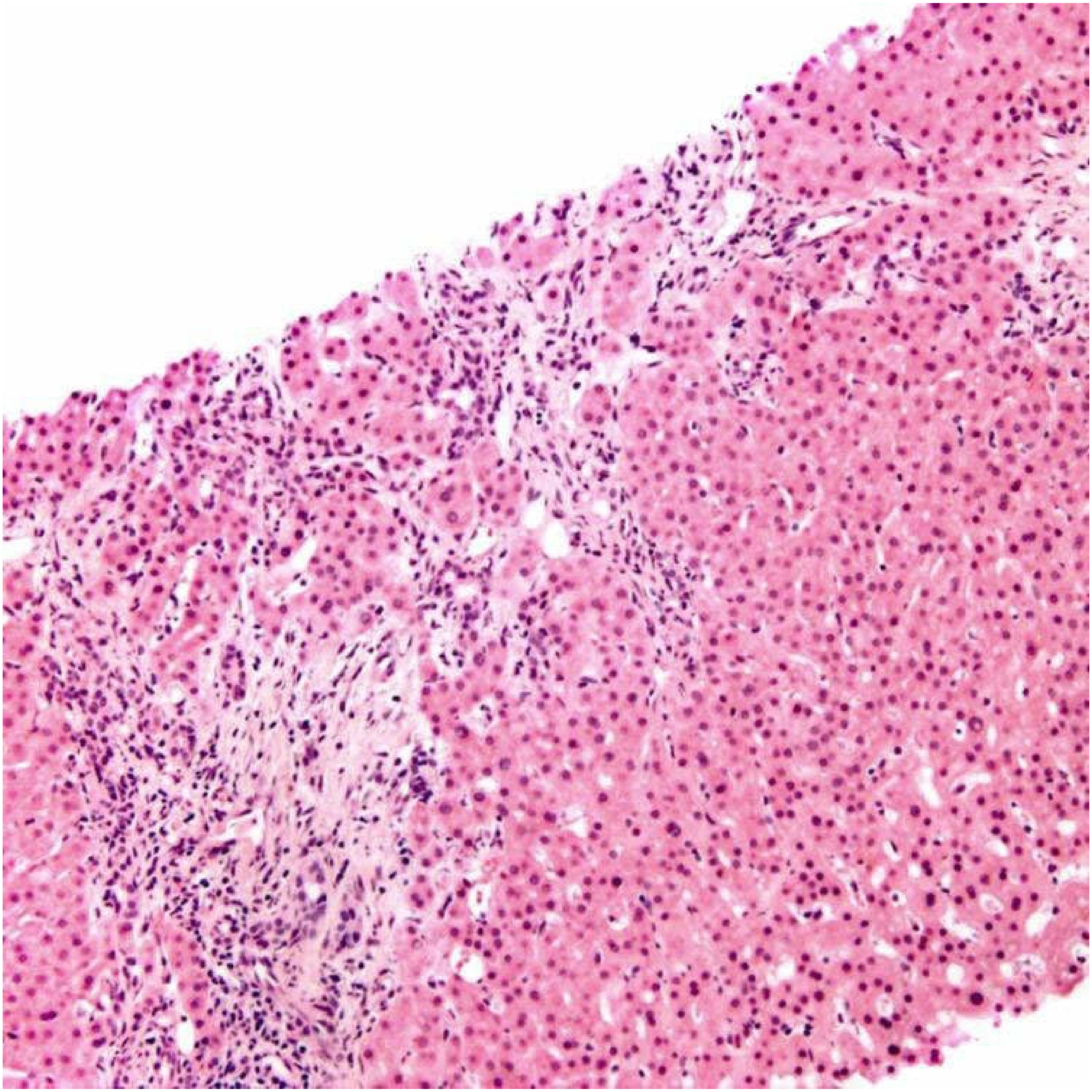


Duct Loss

This portal tract shows hepatic artery branches ⇨ without an accompanying bile duct, indicative of duct loss. Note the surrounding ductular reaction as well as cholestasis →, which typically does not appear until late in the course of disease.

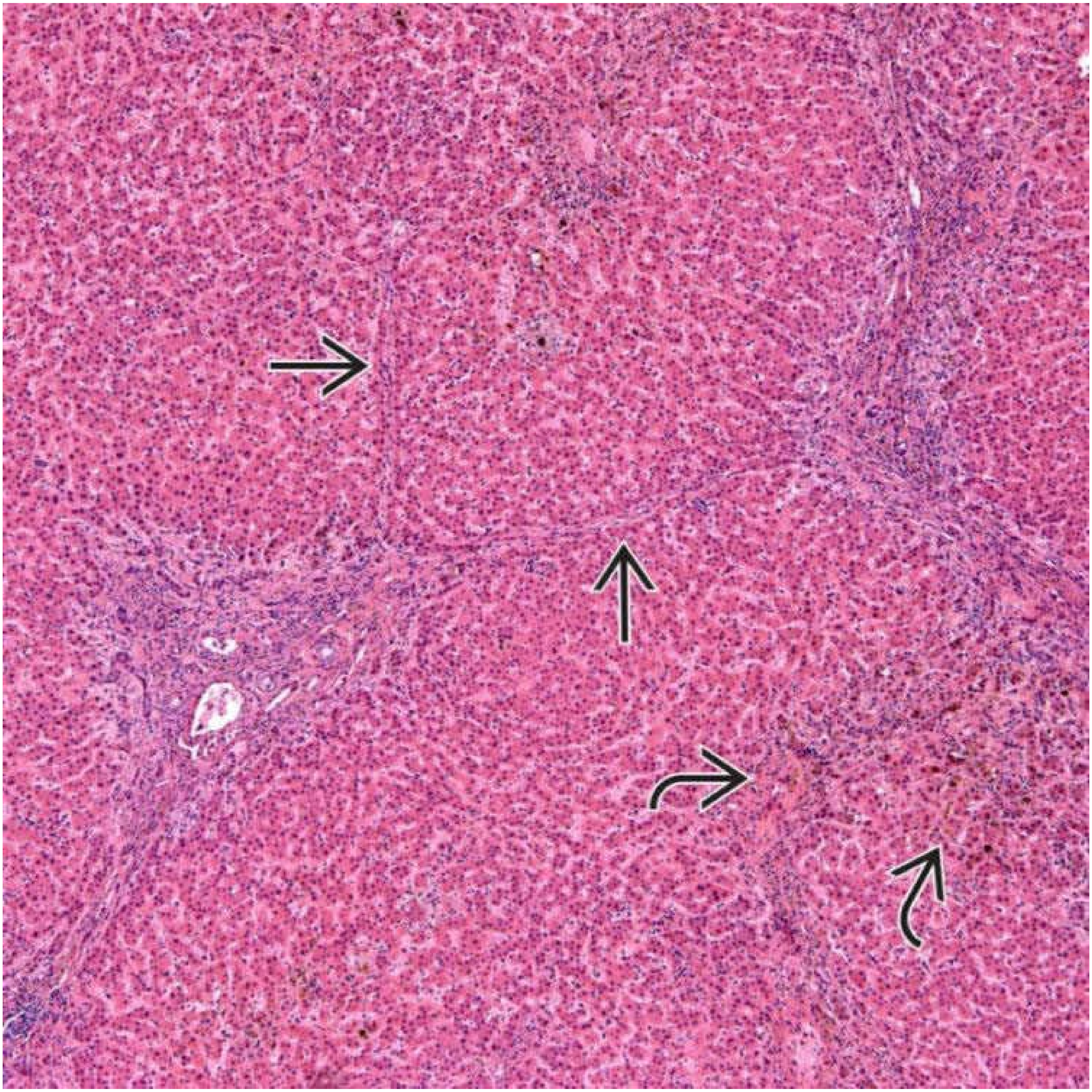


Copper Deposition
Periportal copper deposition → is indicative of chronic cholestasis and can be a helpful finding in the diagnosis of PSC.



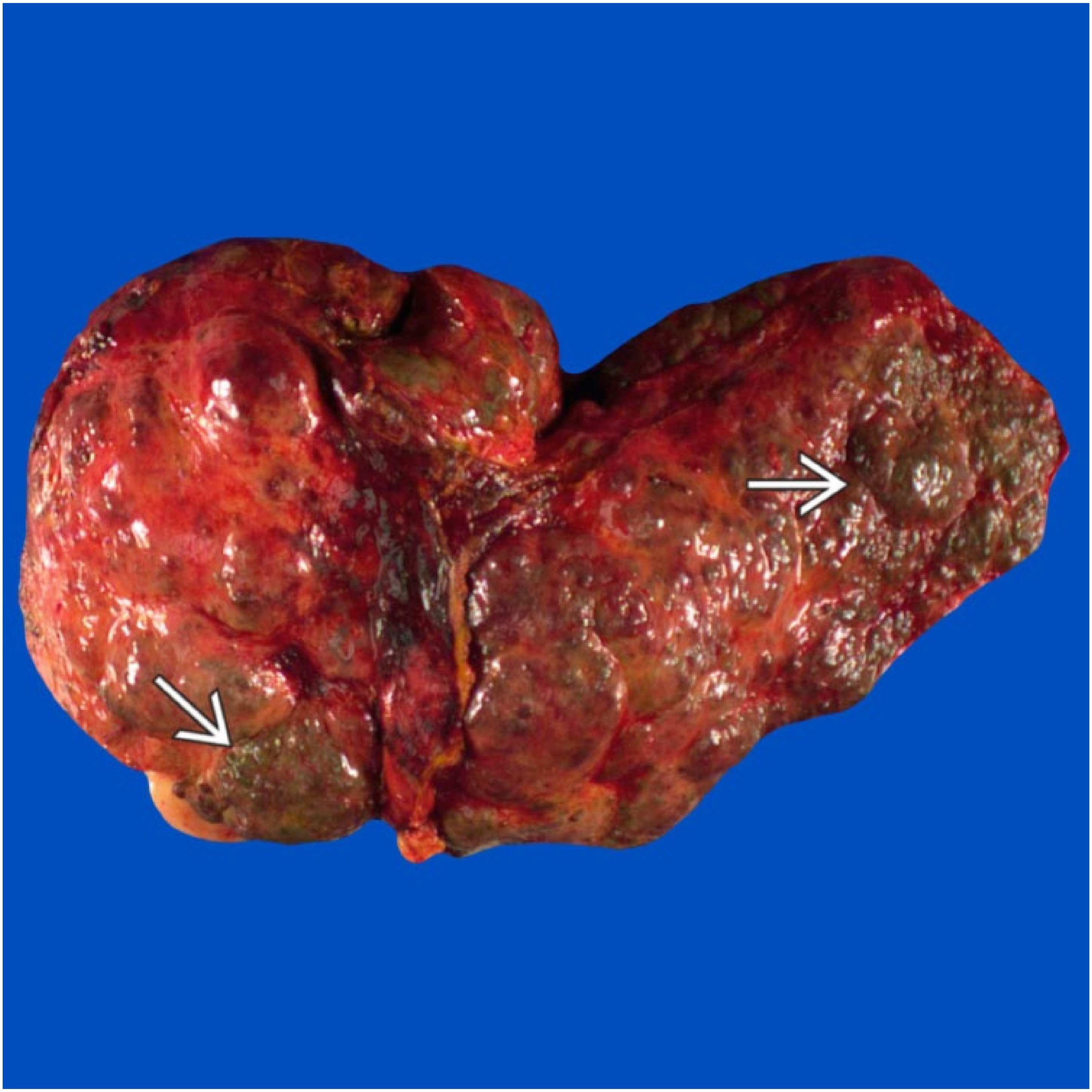
Portal Fibrosis

This liver biopsy from a patient with PSC shows irregular expansion of the portal tract with portal and periportal fibrosis. There is mild associated lymphocytic portal inflammation as well as ductular reaction. As is typical of PSC, there is very little lobular inflammation.

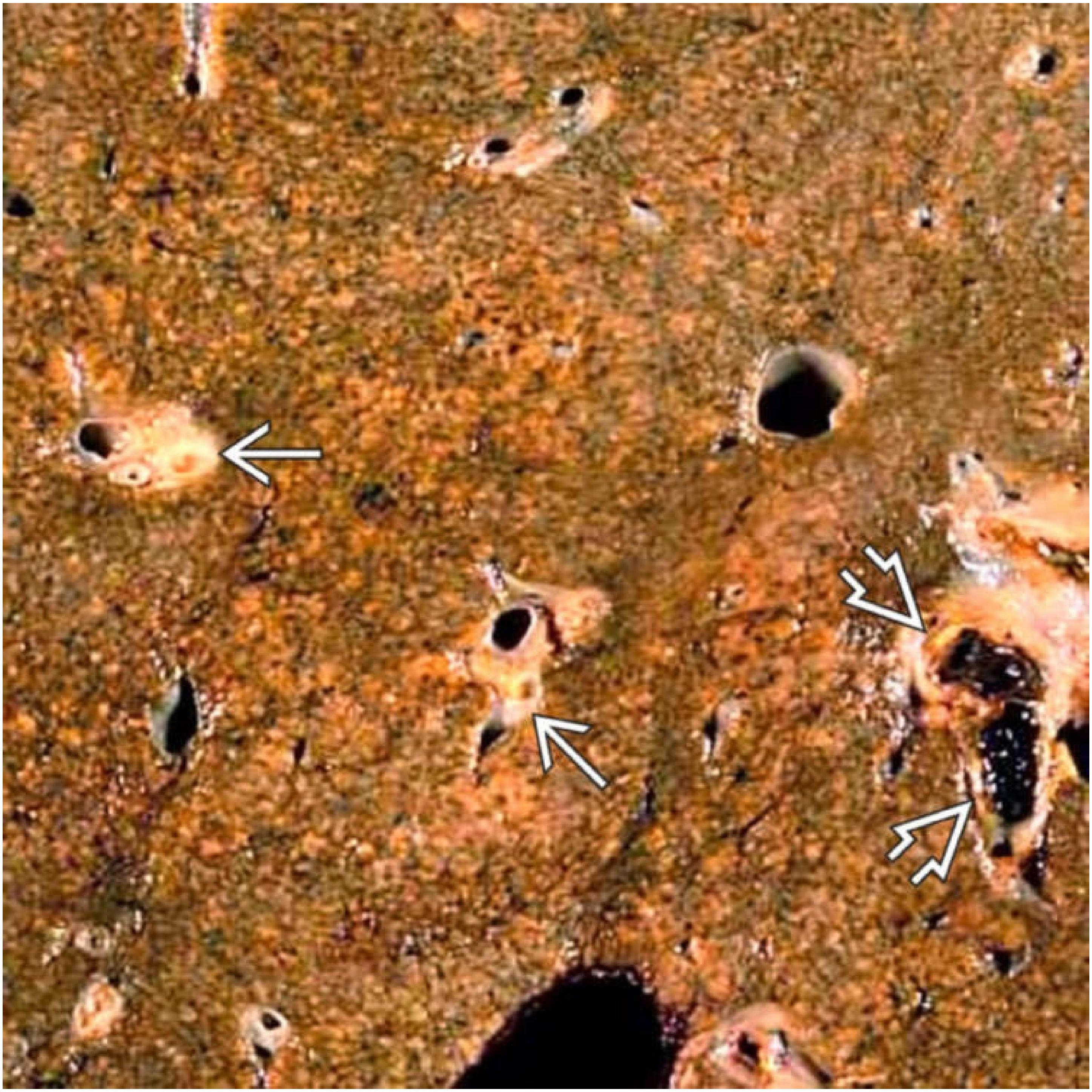


Septal Fibrosis

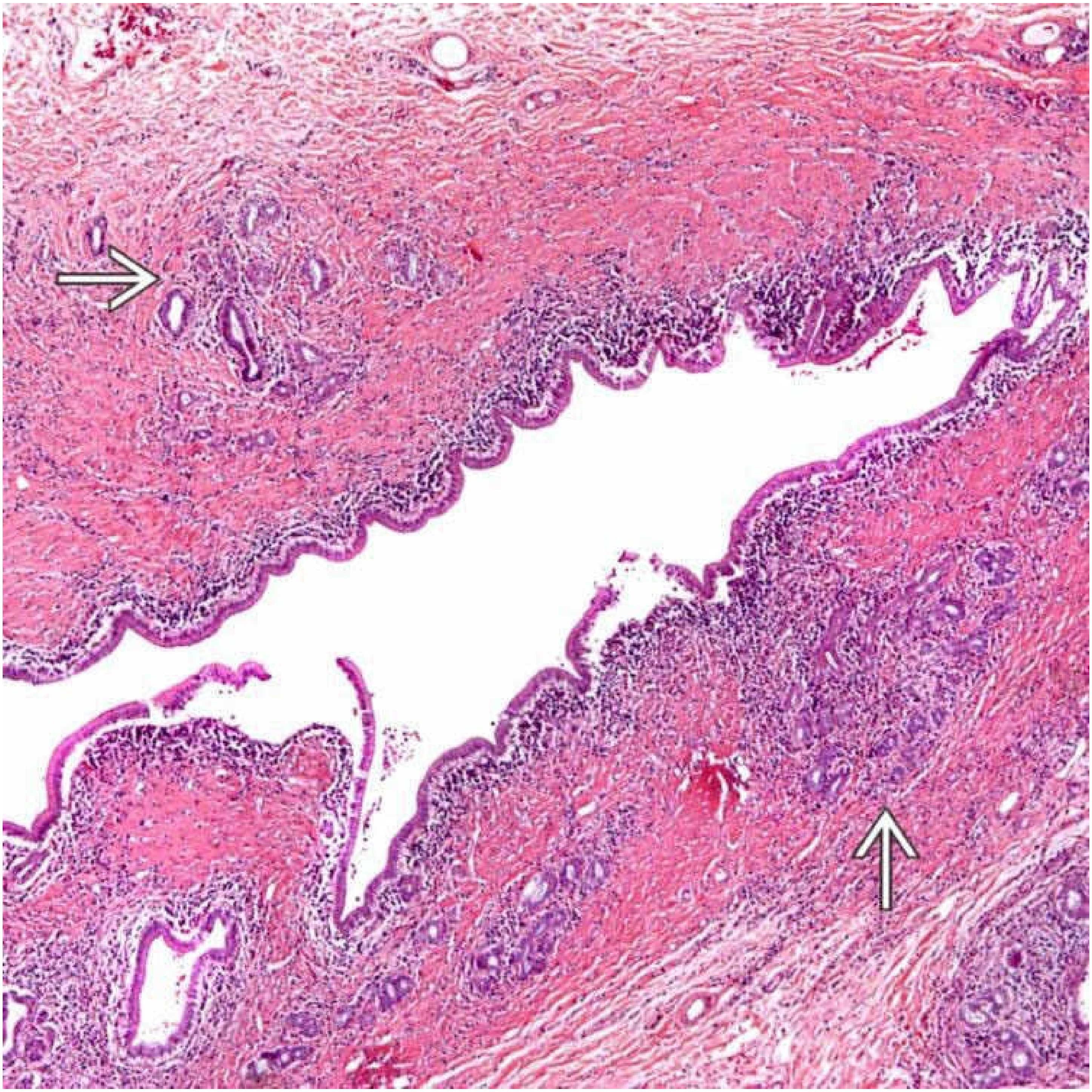
This case of PSC shows irregular portal expansion with the formation of fibrous septa →. There is surrounding ductular reaction as well as cholestasis ↷ .



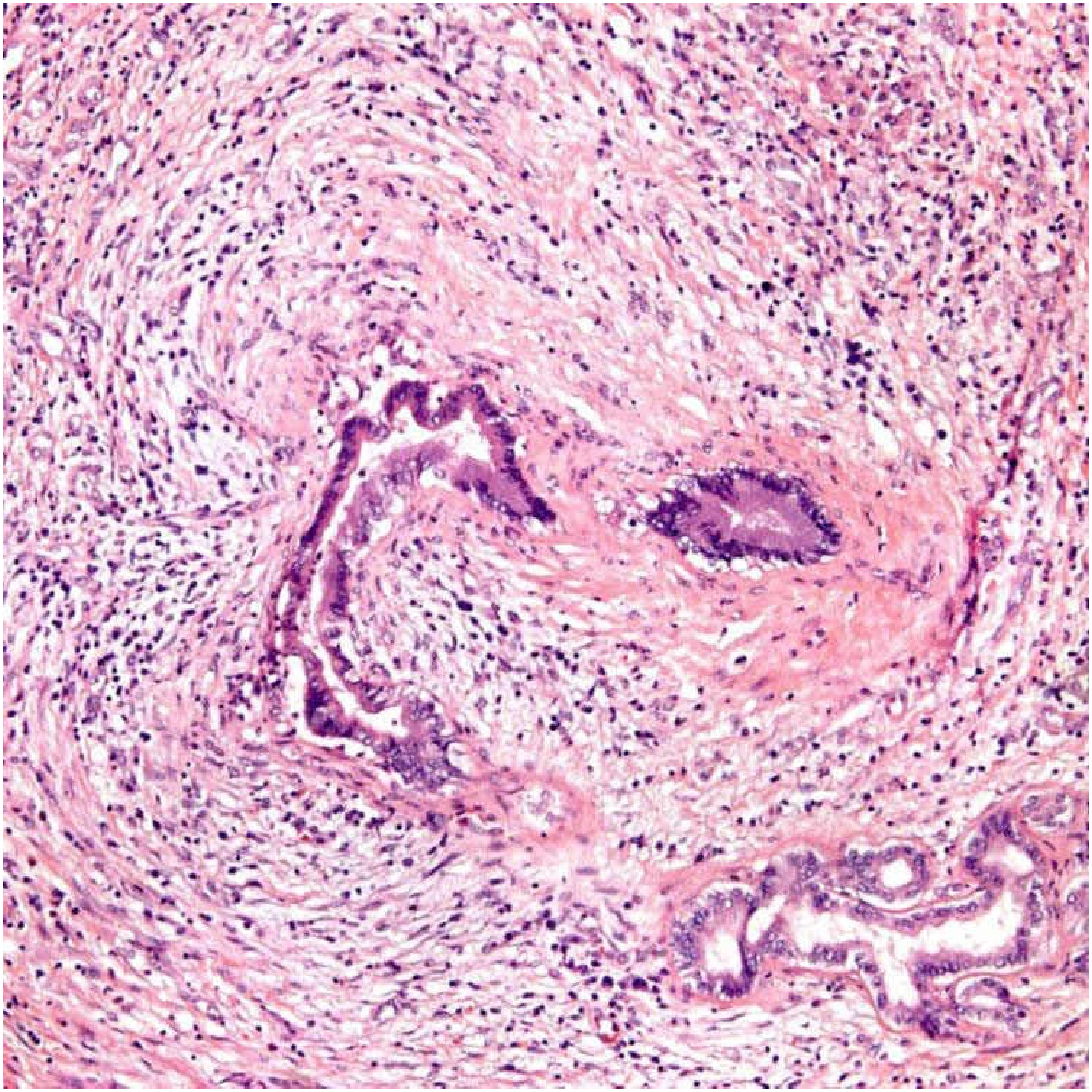
Cirrhosis
An explanted liver from a patient with PSC shows biliary cirrhosis. The liver contour is irregular, shrunken, and firm and shows diffuse, variably sized green nodules ⇒, reflecting marked cholestasis.



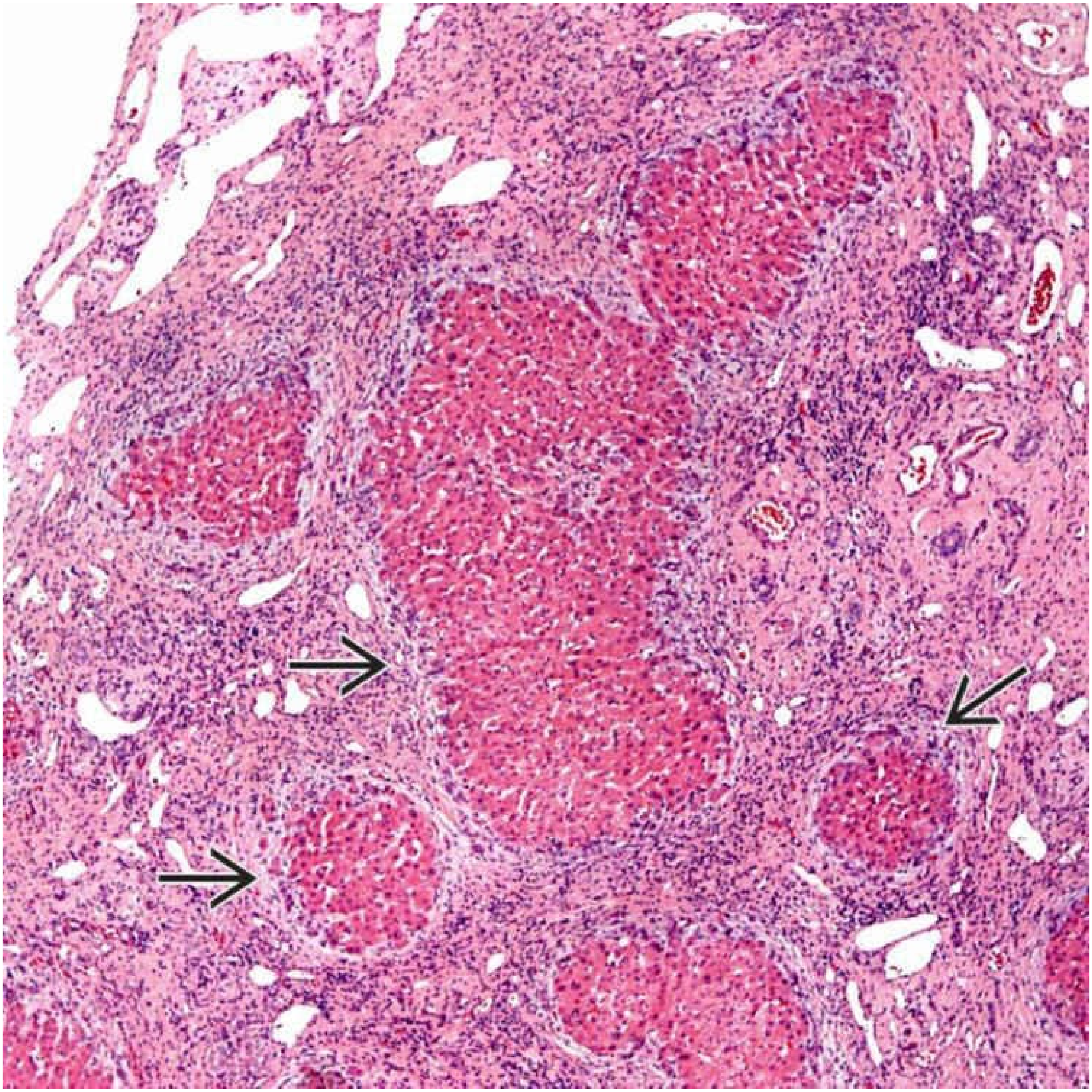
Cirrhosis, Gross Cut Surface
The cut surface of an explanted liver shows biliary cirrhosis with diffuse nodularity. There is thickening of the walls of the large- and medium-sized bile ducts ⇨ due to periductal fibrosis. Inspissated bile sludge is present in dilated ducts ⇨ .



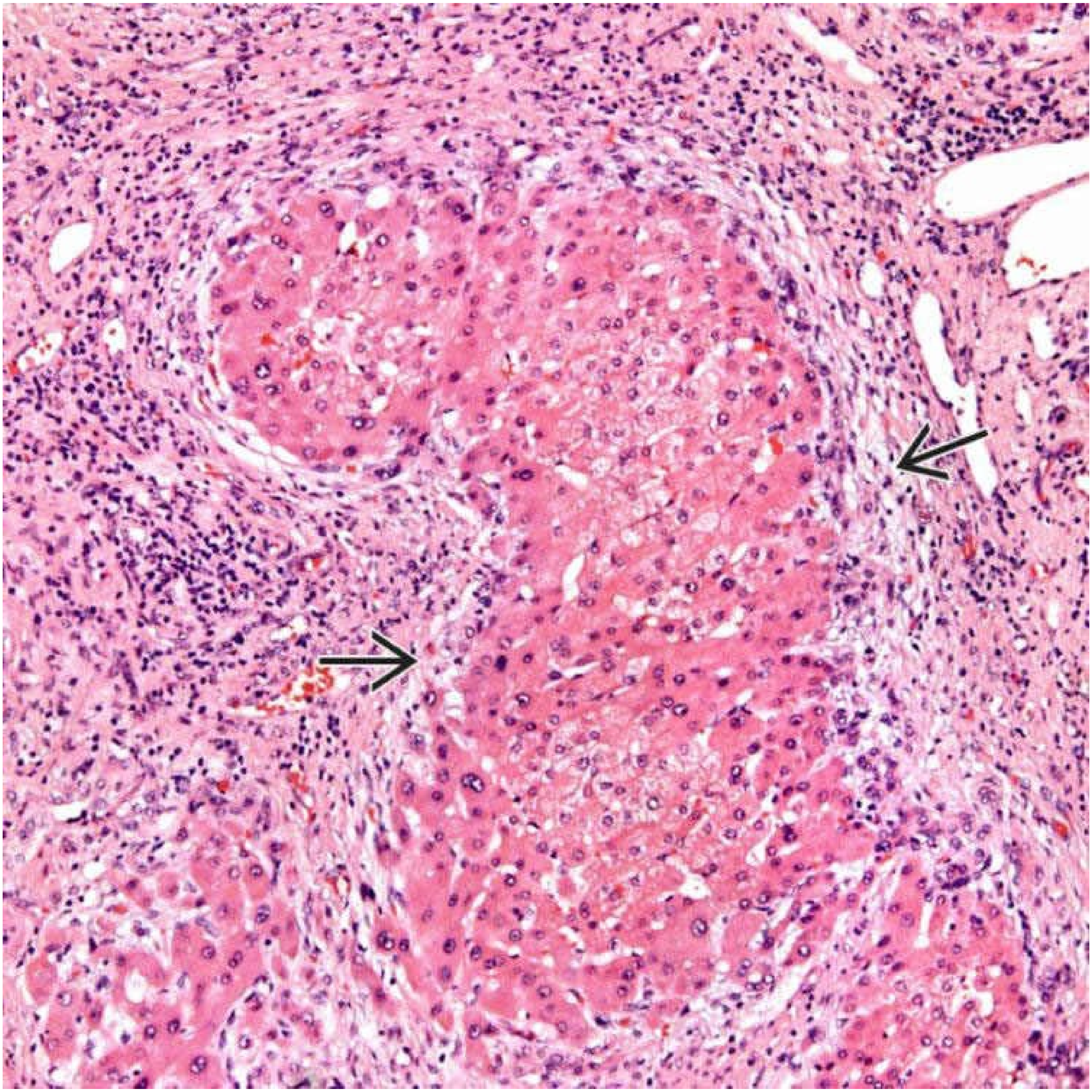
Inflammation of Large Ducts
This section from the hilum of an explanted liver illustrates large duct involvement by PSC. The duct is surrounded by a marked lymphoplasmacytic infiltrate that extends to involve the smaller lobules of ducts ⇒ around the larger duct profile.



Large Duct Involvement
This large duct involved by PSC shows periductal fibrosis, a surrounding lymphoplasmacytic infiltrate that extends into the ductal epithelium, and epithelial damage.

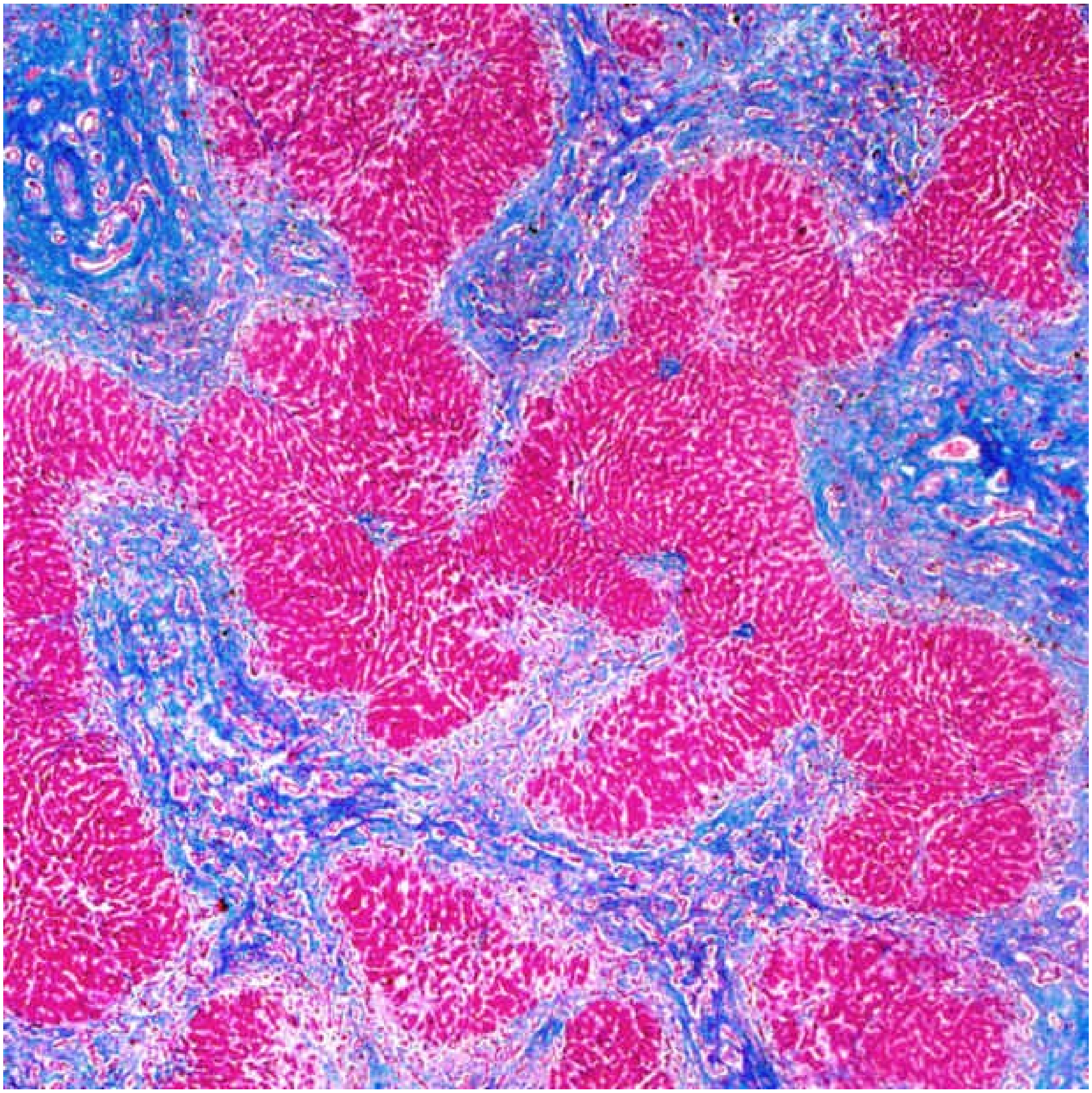


Biliary Cirrhosis
Cirrhosis in the context of PSC is typical of biliary cirrhosis in general, with irregular, jigsaw puzzle-shaped or geographic nodules. The ductular reaction and cholate stasis may produce a pale, halo effect around the periphery of the nodules as well →.



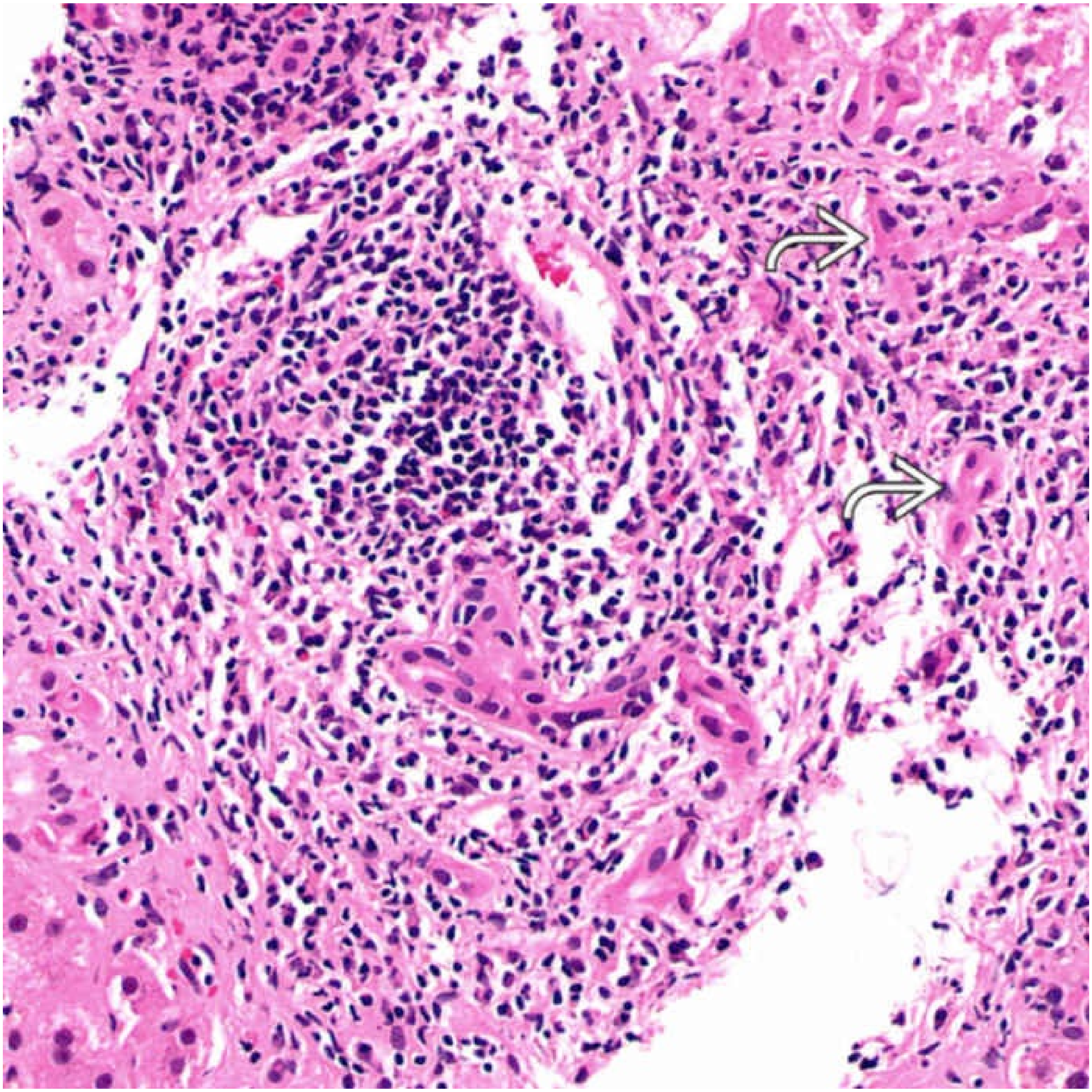
Cirrhosis With Halo

At higher power, the halo around the cirrhotic nodules in biliary cirrhosis, caused by ductular reaction, edema, and cholate stasis, is even more evident →. Surrounding fibrous bands contain a lymphoplasmacytic infiltrate.

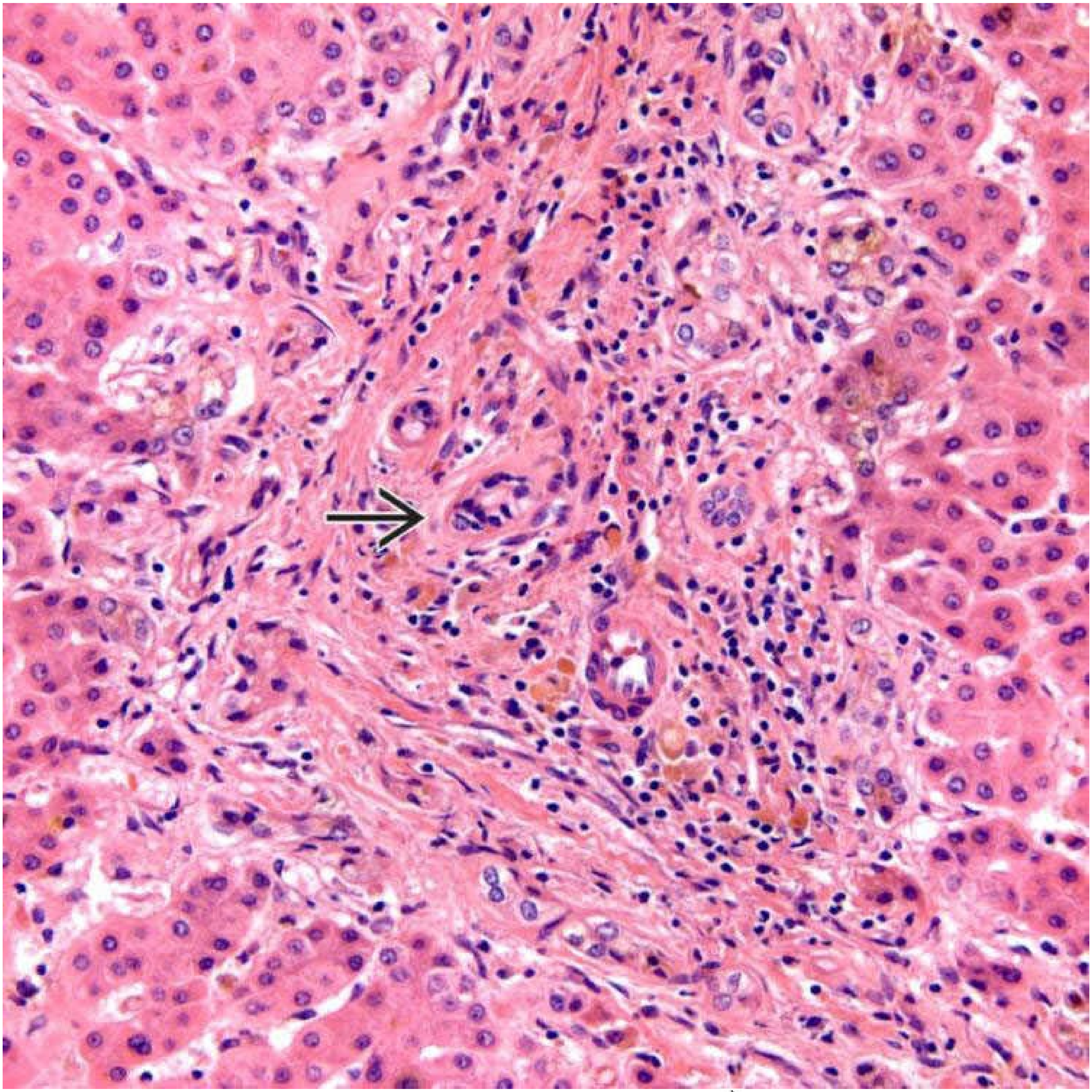


Biliary Cirrhosis, Trichrome Stain

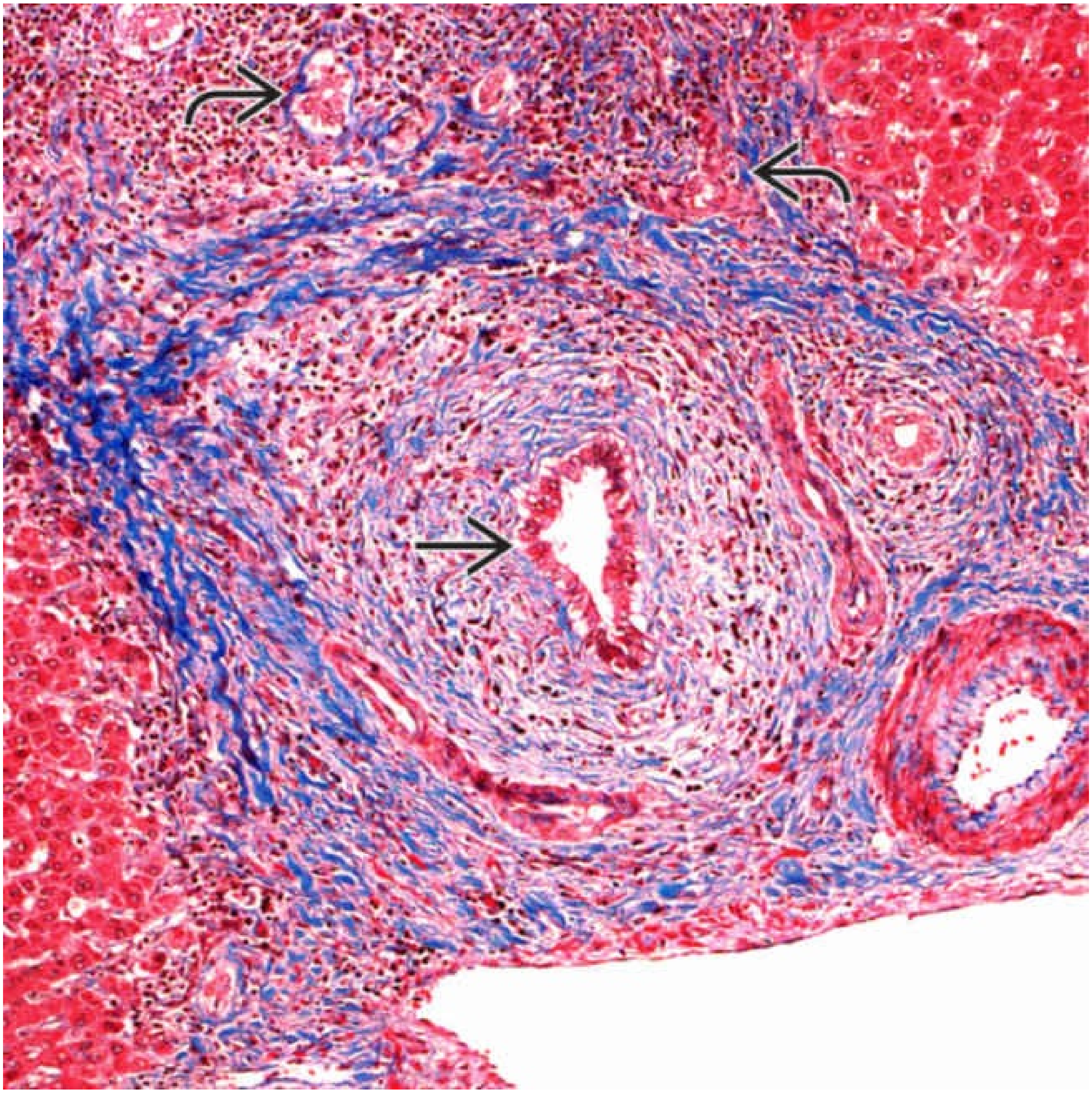
Trichrome staining emphasizes the characteristic pattern of biliary cirrhosis with a geographic, jigsaw puzzle- or garland-shaped nodular pattern. This pattern is typical of biliary cirrhosis in the context of PSC.



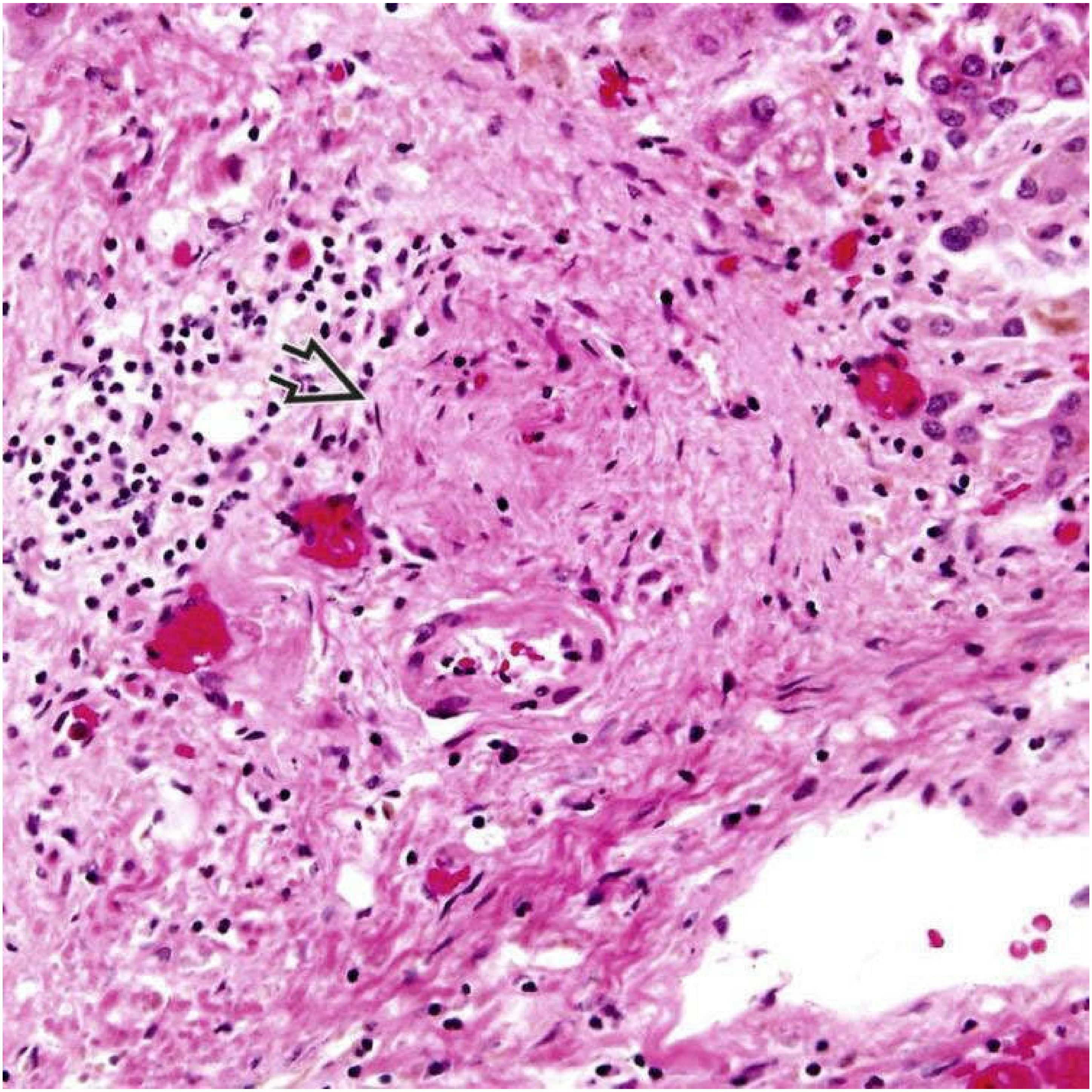
Recurrent Disease Post Transplant
A case of recurrent PSC (3 years post liver transplantation) shows bile duct damage with portal lymphocytic infiltration. Ductular reaction and the lack of definite endotheliitis help differentiate PSC from acute cellular rejection, although the distinction can be difficult.



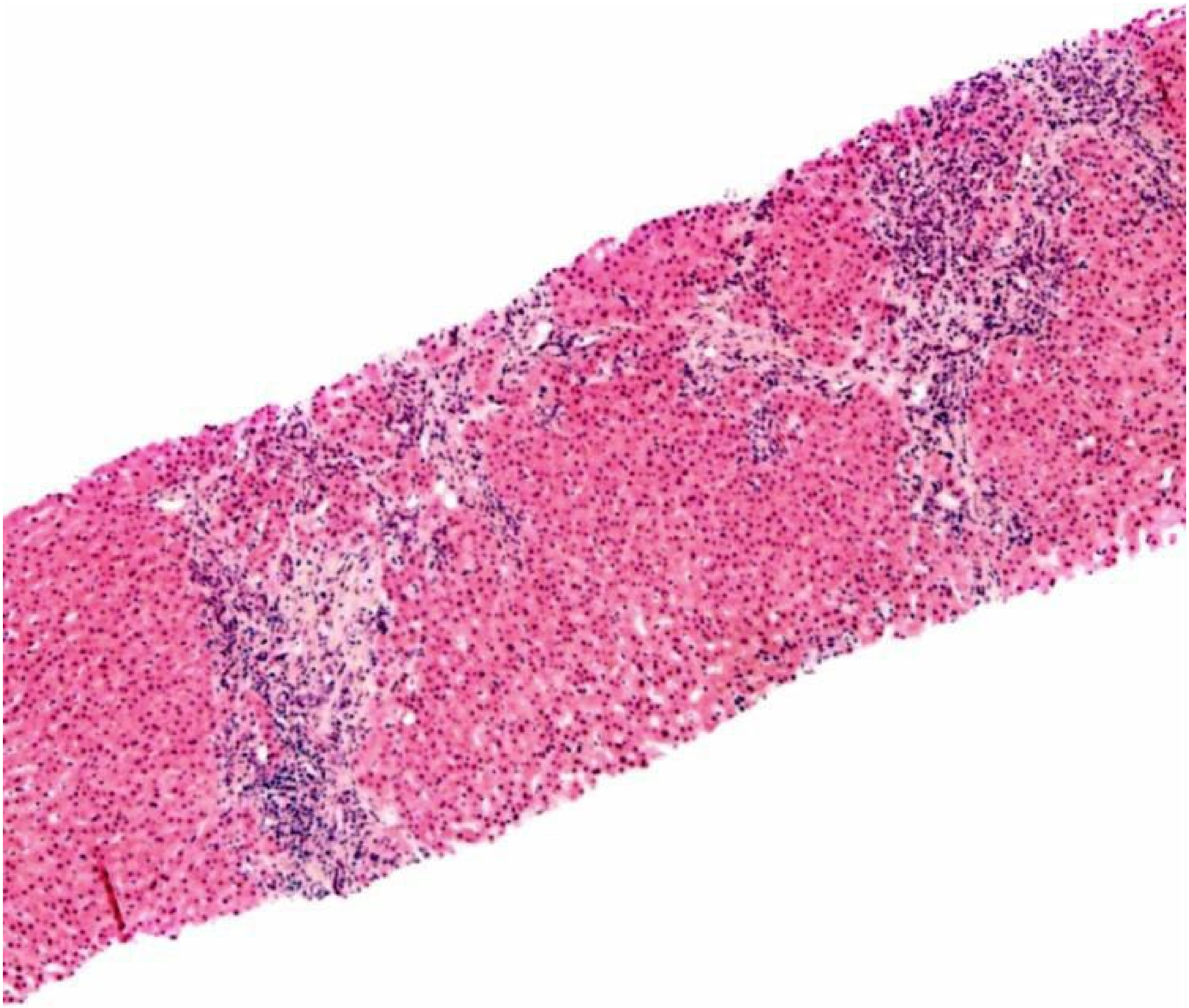
Portal tracts show mild lymphocytic inflammation, duct atrophy →, and ductular reaction.



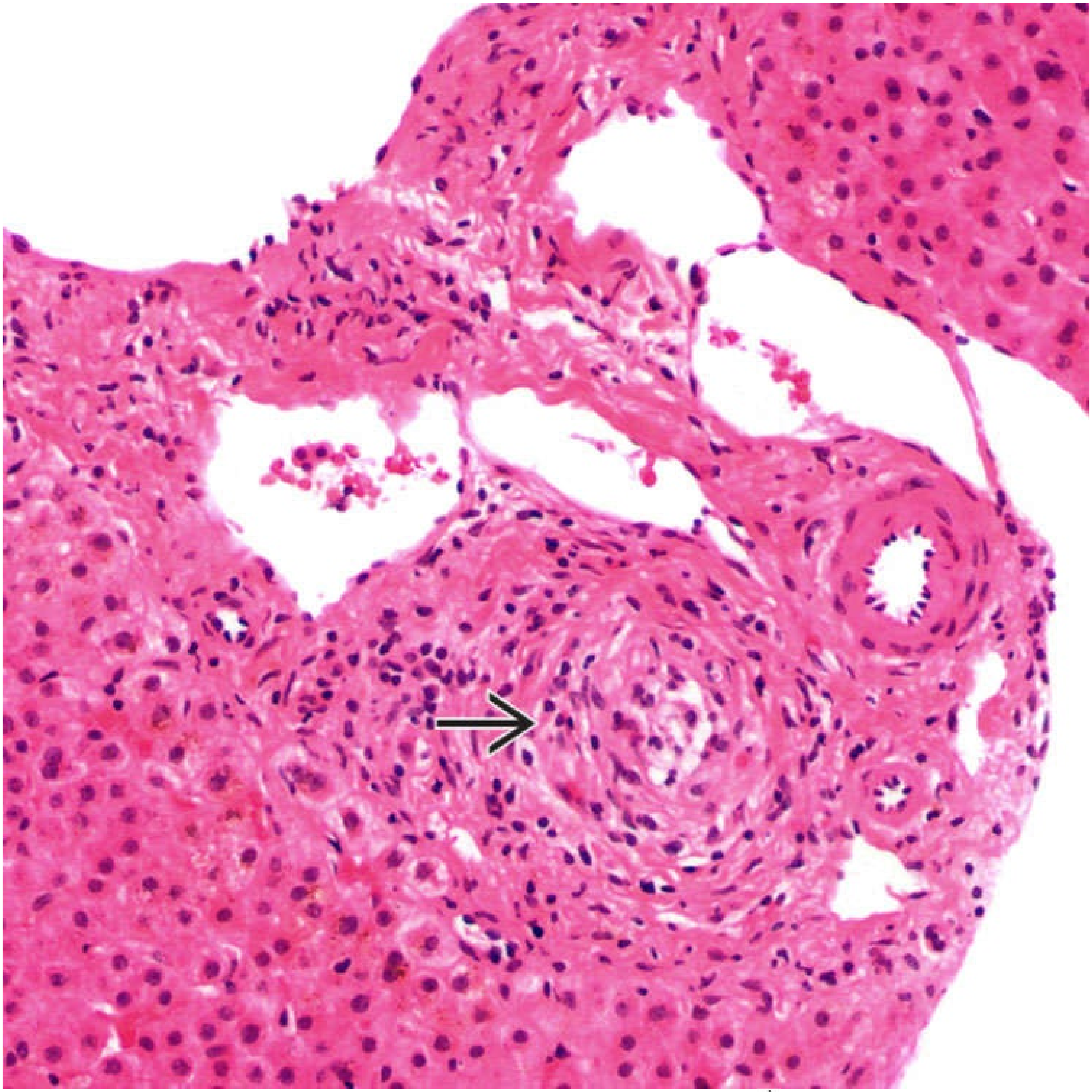
Trichrome stain highlights onion skin-type periductal fibrosis, characteristic of PSC. The duct epithelium is atrophic →. There is a mild lymphocytic infiltrate in the portal tract and mild ductular reaction ↷ in the periportal area.



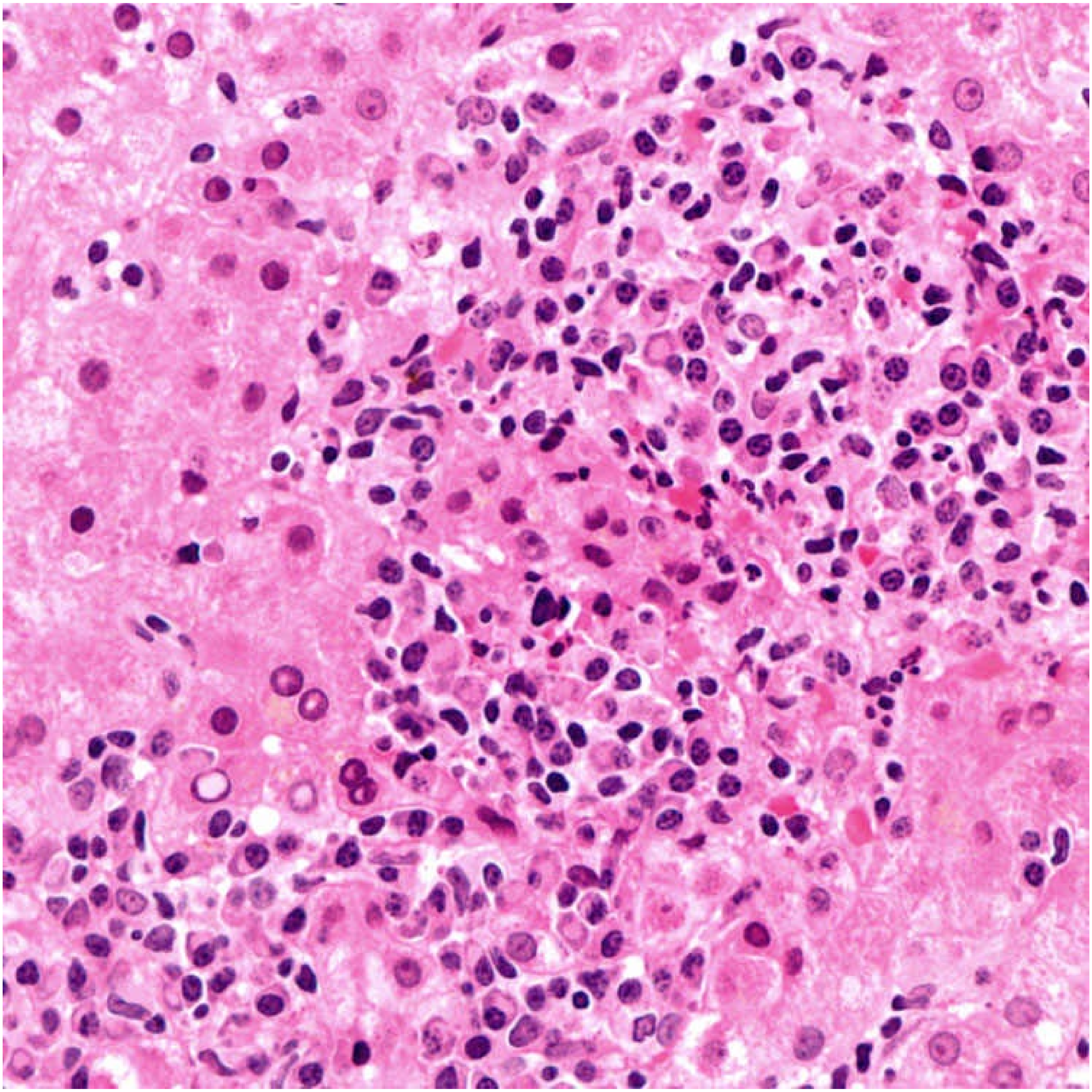
This portal tract shows an intact hepatic artery branch but no accompanying interlobular bile duct. There is only a residual, somewhat nodular scar ➪. Accompanying inflammation is very mild.



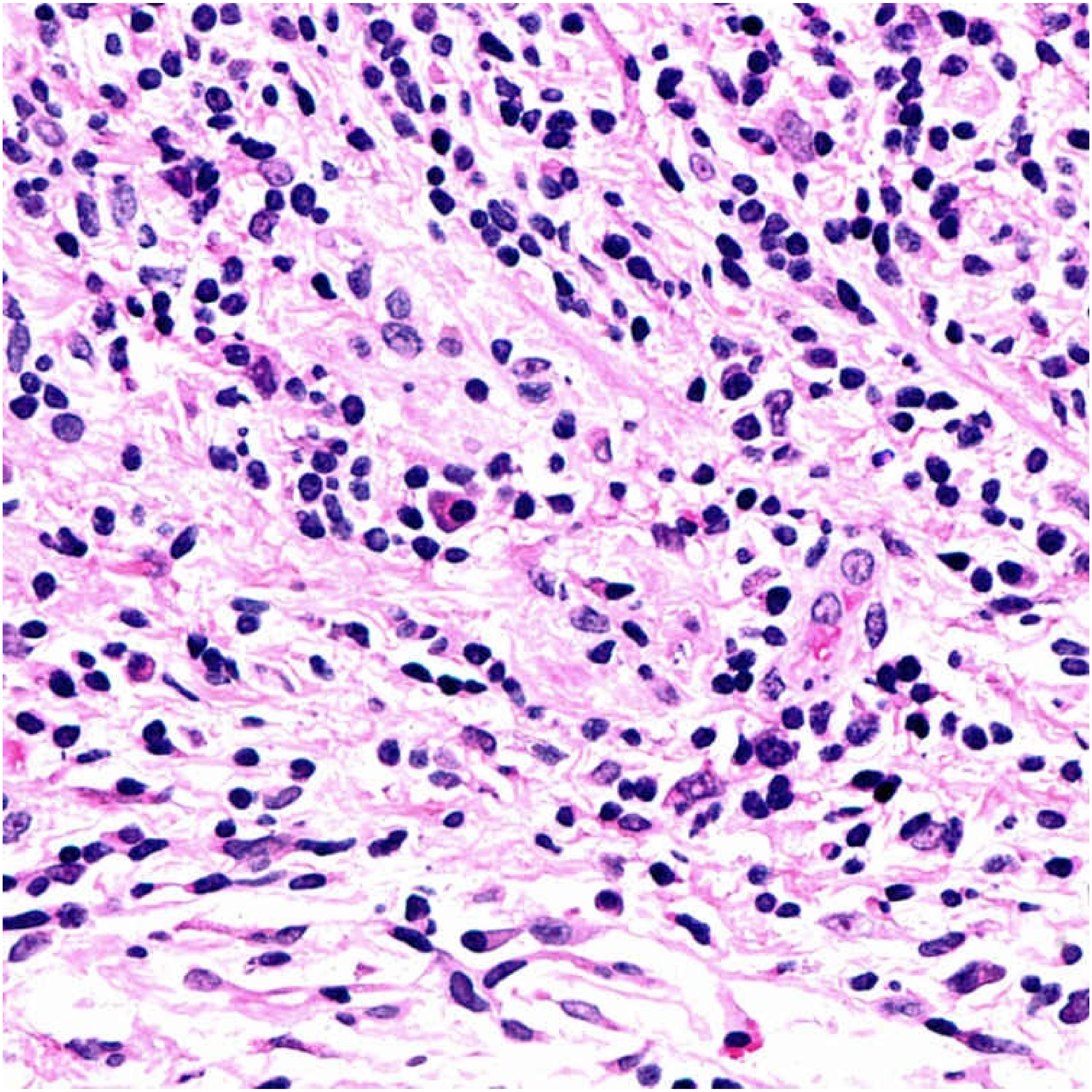
This low-power photomicrograph of a liver biopsy from a patient with PSC shows irregular portal/periportal expansion with early fibrous septa formation.



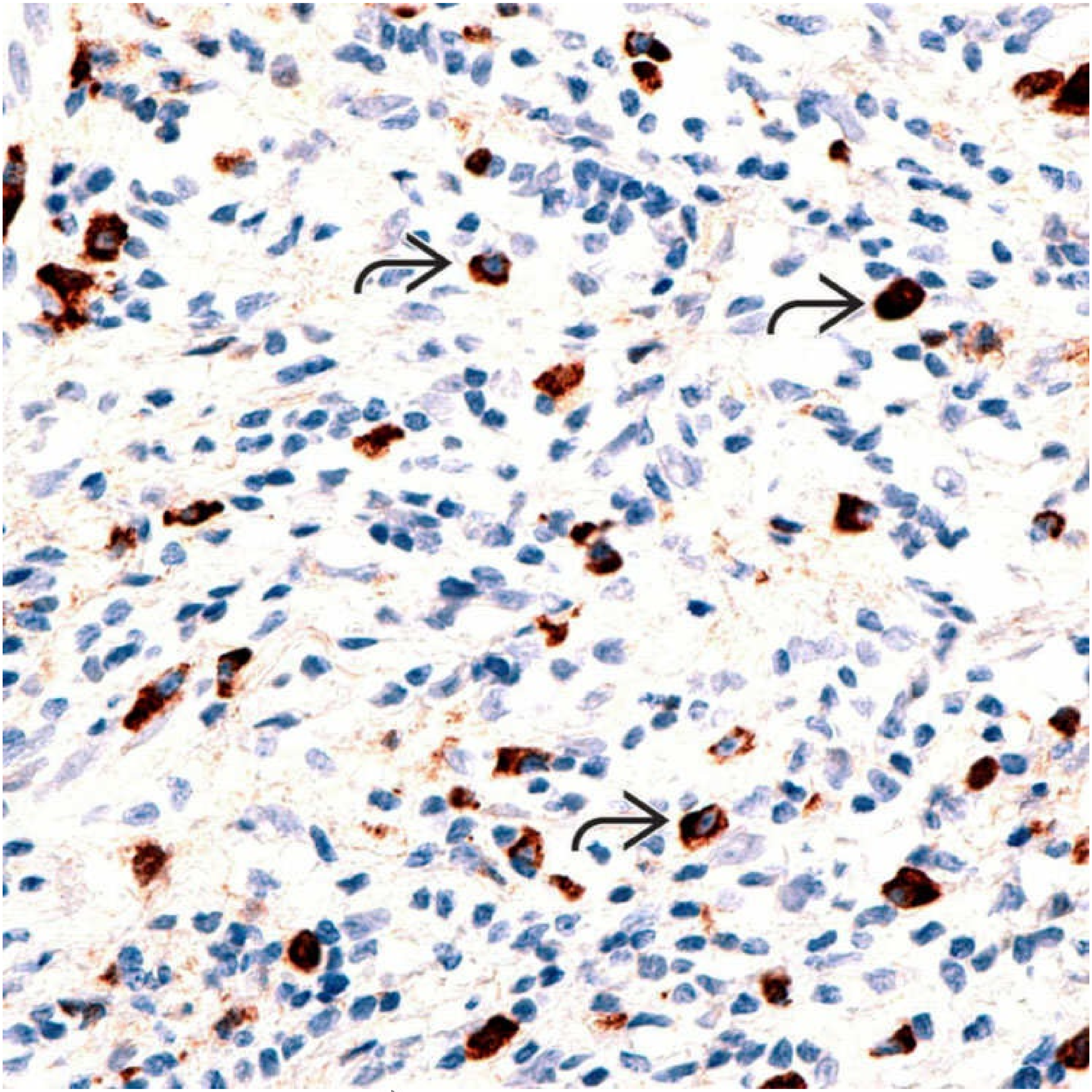
A case of HIV cholangiopathy shows ductopenia with mild laminar fibrosis →. No infectious agents are demonstrated in this biopsy. Only rare inflammatory cells are present.



Autoimmune hepatitis-PSC overlap syndrome typically shows more pronounced interface and lobular activity than that seen in PSC alone. Note the presence of abundant plasma cells as well. Characteristic features of PSC were also present in this case.



This biopsy of a strictured extrahepatic bile duct shows a dense lymphoplasmacytic infiltrate, typical of IgG4-associated cholangitis. The biliary stricture was thought to be malignant endoscopically. A pancreatic mass was also present in this case.



Numerous IgG4(+) plasma cells are demonstrated by immunohistochemical stain in this bile duct biopsy, confirming the diagnosis of IgG4-associated cholangitis. IgG4-associated cholangitis can mimic PSC both clinically and radiographically.

SELECTED REFERENCES

1. Bonato, G, et al. Malignancies in primary sclerosing cholangitis – a continuing threat. *Dig Dis*. 2015; 33(Suppl 2):140–148.
2. Ponsioen, CY. Diagnosis, differential diagnosis, and epidemiology of primary sclerosing cholangitis. *Dig Dis*. 2015; 33(Suppl 2):134–139.
3. Ananthakrishnan, AN, et al. Mortality and extraintestinal cancers in patients with primary sclerosing cholangitis and inflammatory bowel disease. *J Crohns Colitis*. 2014; 8(9):956–963.
4. Eaton, JE, et al. Pathogenesis of primary sclerosing cholangitis and advances in diagnosis and

management. *Gastroenterology*. 2013; 145(3):521–536.
5. Hirschfield, GM, et al. Primary sclerosing cholangitis. *Lancet*. 2013; 382(9904):1587–1599.
6. Singh, S, et al. Primary sclerosing cholangitis: diagnosis, prognosis, and management. *Clin Gastroenterol Hepatol*. 2013; 11(8):898–907.
7. Devarbhavi, H, et al. HIV/AIDS cholangiopathy: clinical spectrum, cholangiographic features and outcome in 30 patients. *J Gastroenterol Hepatol*. 2010; 25(10):1656–1660.
8. Karlsen, TH, et al. Update on primary sclerosing cholangitis. *Dig Liver Dis*. 2010; 42(6):390–400.
9. Alderlieste, YA, et al. Immunoglobulin G4-associated cholangitis: one variant of immunoglobulin G4-related systemic disease. *Digestion*. 2009; 79(4):220–228.
10. Deshpande, V, et al. IgG4-associated cholangitis: a comparative histological and immunophenotypic study with primary sclerosing cholangitis on liver biopsy material. *Mod Pathol*. 2009; 22(10):1287–1295.
11. Duclos-Vallee, JC, et al. Recurrence of autoimmune disease, primary sclerosing cholangitis, primary biliary cirrhosis, and autoimmune hepatitis after liver transplantation. *Liver Transpl*. 2009; 15(Suppl 2):S25–S34.
12. Silveira, MG, et al. Primary sclerosing cholangitis. *Can J Gastroenterol*. 2008; 22(8):689–698.
13. Weismüller, TJ, et al. The challenges in primary sclerosing cholangitis–aetiopathogenesis, autoimmunity, management and malignancy. *J Hepatol*. 2008; 48(Suppl 1):S38–S57.

Ischemic Cholangitis

KEY FACTS

Etiology/Pathogenesis

- Any impairment of hepatic artery or peribiliary vascular plexus blood flow may result in ischemic bile duct injury
  - Manifestations vary with severity and rapidity of ischemic insult
  - Causes include arterial thrombosis, surgical injury, hypotension

Clinical Issues

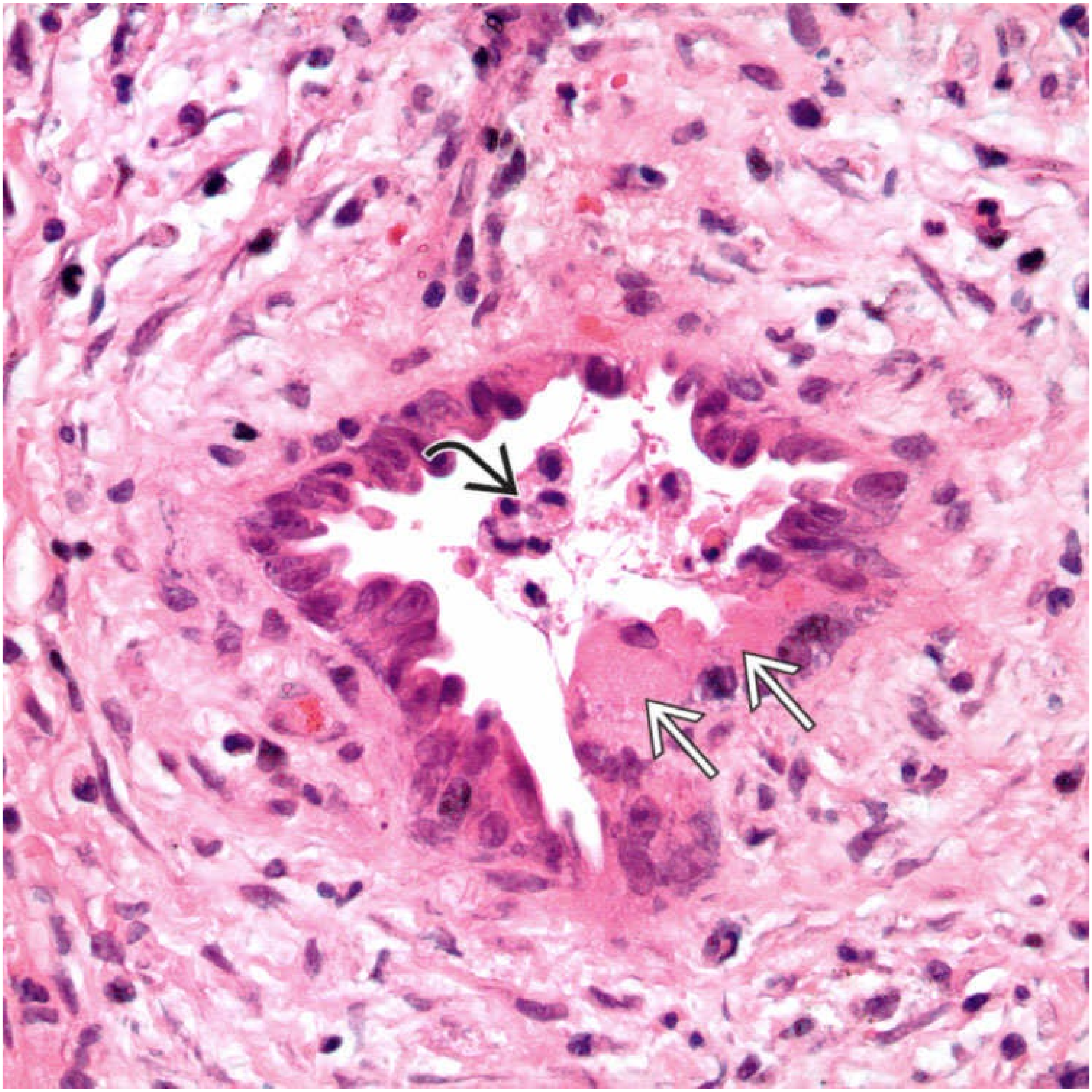
- Prognosis varies depending on rapidity and extent of ischemic insult
  - Severe acute injury may lead to hepatic failure
  - Chronic ischemia leads to progressive obliteration of bile ducts, biliary cirrhosis, liver failure

Imaging

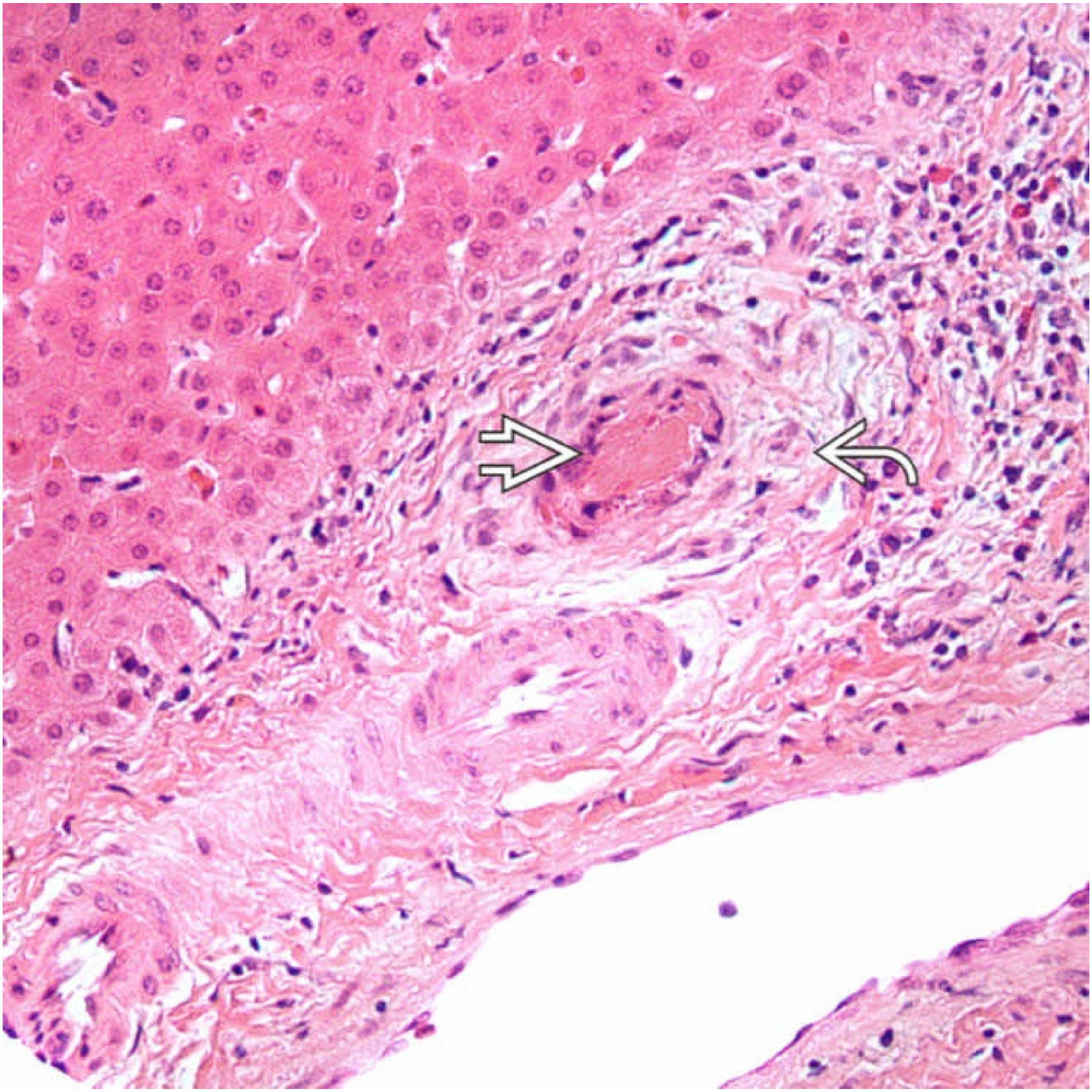
- Acute ischemic injury results in dilated bile ducts with filling defects due to biliary casts
  - In chronic setting, diffuse stricturing and segmental dilatation of biliary tree seen by CT, MR, MRCP, or ERCP
  - Ischemic cholangitis is one cause of secondary sclerosing cholangitis

Microscopic

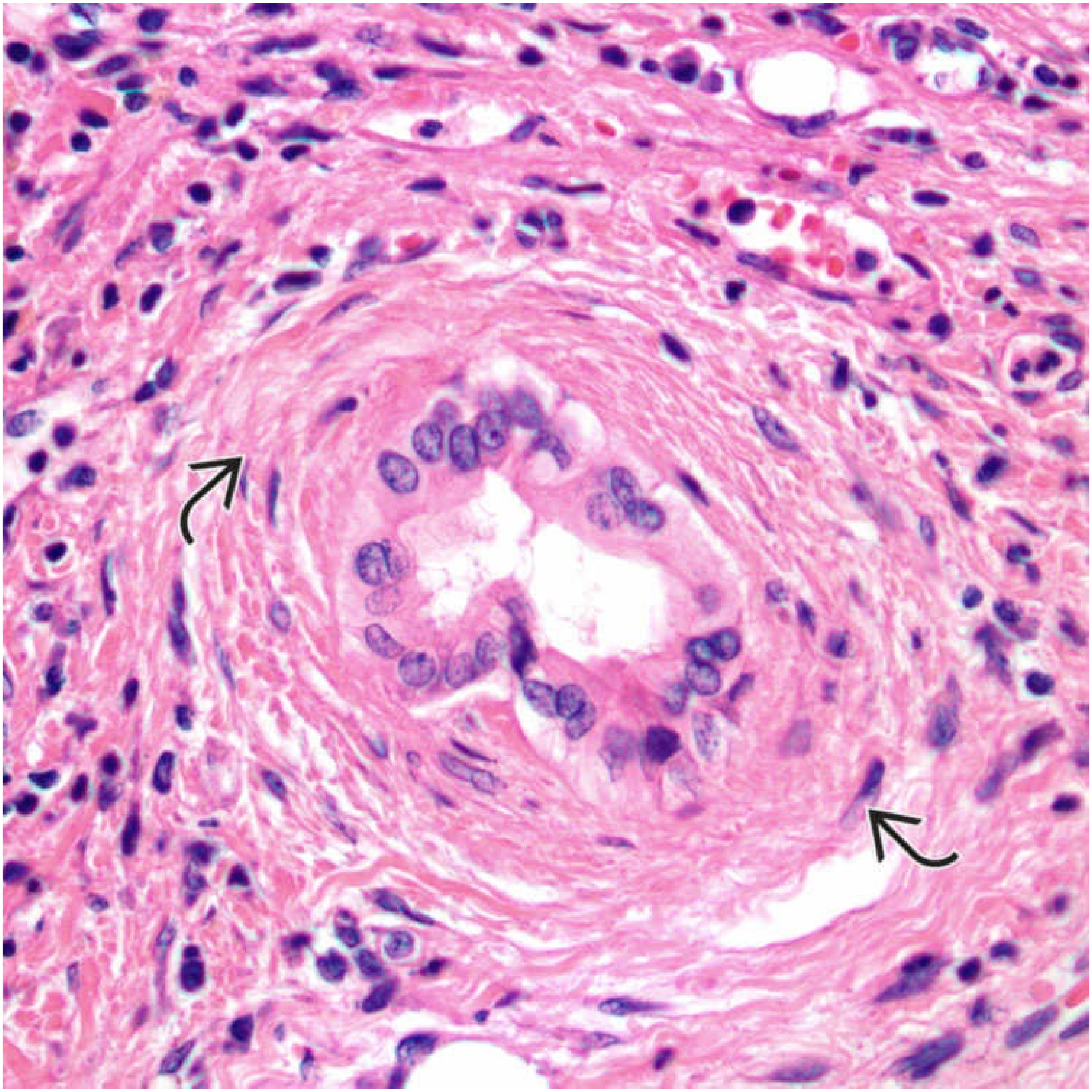
- Acute ischemia
  - Bile duct epithelial cell necrosis and desquamation with formation of biliary casts
  - Bile leaks result in bilomas and bile abscess
- Chronic ischemic injury
  - Atrophy and erosion of large duct epithelium
  - Periductal fibrosis with progressive bile duct loss, stricturing, and fibrosis
  - Secondary features of biliary obstruction
  - Progression to biliary fibrosis or cirrhosis



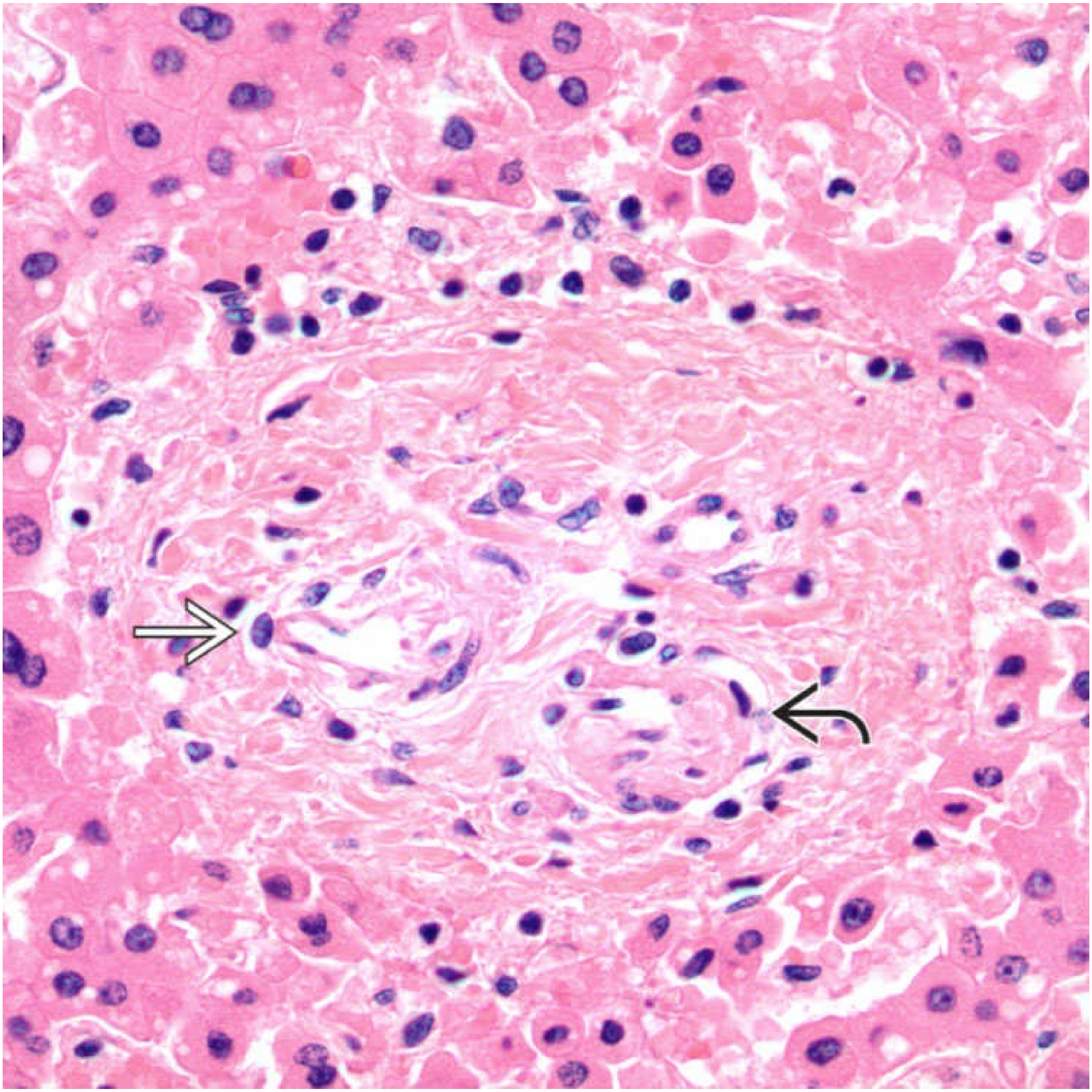
Bile Duct Epithelial Cell Necrosis
Acute ischemic cholangitis features bile duct epithelial cell necrosis, as well as sloughing of epithelial cells into the bile duct lumen to form biliary casts.



Biliary Cast
This injured bile duct contains a brightly eosinophilic biliary cast in a case of acute ischemic cholangitis. There is also mild portal inflammation and periductal edema .



Periductal Fibrosis
The bile duct injury in ischemic cholangitis features uneven nuclear spacing and loss of polarity. There is surrounding periductal fibrosis .



Progressive Bile Duct Loss
Progressive bile duct loss is a feature of chronic ischemic cholangitis. This portal tract contains a hepatic artery and portal vein branches but lacks an identifiable bile duct profile.

TERMINOLOGY

Synonyms

• Ischemic cholangiopathy

Definitions

• Bile duct injury and necrosis due to impaired blood supply of any cause

ETIOLOGY/PATHOGENESIS

Ischemic Bile Duct Injury

- Unlike hepatocytes, intrahepatic biliary tree is entirely dependent on arterial blood supply
  - Impairment of hepatic artery or peribiliary vascular plexus blood flow due to any cause results in ischemic bile duct injury
  - Associated conditions
    – Arterial thrombosis
    – Hypotension
    – Surgical injury to biliary tree/previous transplant
    – CMV-induced endothelial cell injury
- Manifestations vary with severity and rapidity of ischemic insult

CLINICAL ISSUES

Presentation

- Abdominal pain
- Fever
- Jaundice
- Biliary sepsis

Laboratory Tests

- Hyperbilirubinemia
- Elevated alkaline phosphatase

Natural History

- Acute complications include bile duct necrosis with bile leak and bile abscess formation
  - Chronic ischemic injury leads to progressive bile duct obliteration, biliary cirrhosis, liver failure
  - Cholangiocarcinoma may develop as result of chronic biliary injury and cirrhosis

Treatment

- Surgical approaches
  - Revision of hepatic artery anastomosis to improve perfusion
  - Biliary drainage or reconstruction
  - Liver transplantation
- Thrombolysis
- Often cannot be treated

Prognosis

- Varies depending on rapidity and extent of ischemic insult

- In severe and rapid cases, may lead to acute hepatic failure
- Consequences lessened by presence or development of collateral circulation
- Liver transplant recipients with ischemic cholangitis may require retransplantation

IMAGING

Radiographic Findings

- Acute ischemic injury results in dilated bile ducts with filling defects due to biliary casts
  - Intrahepatic bilomas may be seen
  - In chronic setting, diffuse stricturing and segmental dilatation of biliary tree seen by CT, MR, MRCP, or ERCP
  - Ischemic cholangitis is one cause of secondary sclerosing cholangitis

MICROSCOPIC

Histologic Features

- Vary with location, timing, and extent of injury
  - Acute
  - Bile duct epithelial cell necrosis and desquamation with formation of biliary casts
  - Bile duct contents may leak through wall of necrotic duct into adjacent portal tract or parenchyma, causing necrosis and biloma formation
  - Biloma may become infected, resulting in bile abscess
- Chronic
  - Atrophy and erosion of large duct epithelium
  - Periductal fibrosis with progressive bile duct loss
  - Biliary strictures and cholangiectases
  - Secondary features of biliary obstruction
    - Cholestasis, portal edema, and bile infarcts
  - Portal inflammation usually mild
  - Progressive development of biliary fibrosis or cirrhosis

DIFFERENTIAL DIAGNOSIS

Primary Sclerosing Cholangitis

- Histologically similar to chronic ischemic cholangitis
- Associated with inflammatory bowel disease
- Lacks history/risk factors for ischemic cholangitis

Cholangiocarcinoma

- Usually produces more focal bile duct narrowing than ischemic cholangitis

Other Forms of Secondary Sclerosing Cholangitis

- Choledocholithiasis
- Recurrent pyogenic cholangitis
- Congenital disorders (choledochal cyst, Caroli disease)
- Fungal infection with invasion or colonization of biliary tree
- Biliary parasites

SELECTED REFERENCES

1. Mourad, MM, et al. Aetiology and risk factors of ischaemic cholangiopathy after liver transplantation. *World J Gastroenterol*. 2014; 20(20):6159–6169.
2. Imam, MH, et al. Secondary sclerosing cholangitis: pathogenesis, diagnosis, and management. *Clin Liver Dis*. 2013; 17(2):269–277.
3. Ruemmele, P, et al. Secondary sclerosing cholangitis. *Nat Rev Gastroenterol Hepatol*. 2009; 6(5):287–295.
4. Deltenre, P, et al. Ischemic cholangiopathy. *Semin Liver Dis*. 2008; 28(3):235–246.
5. Zilkens, C, et al. Hepatic failure after injury – a common pathogenesis with sclerosing cholangitis? *Eur J Med Res*. 2008; 13(7):309–313.
6. Kaczmarek, B, et al. Ischemic cholangiopathy after liver transplantation from controlled non-heart-beating donors-a single-center experience. *Transplant Proc*. 2007; 39(9):2793–2795.
7. Lee, HW, et al. Classification and prognosis of intrahepatic biliary stricture after liver transplantation. *Liver Transpl*. 2007; 13(12):1736–1742.

Large Bile Duct Obstruction

KEY FACTS

Terminology

- Large bile duct obstruction (LBDO): Mechanical blockage of extrahepatic or large intrahepatic bile ducts
  - Changes on liver biopsy are secondary to obstructive biliary process
  - Usually clinical and radiographic diagnosis
    – Liver biopsy often unnecessary unless clinical findings/radiographic studies equivocal or misleading

Etiology/Pathogenesis

- Multifactorial
  - Gallstones, neoplasms/masses, strictures, sclerosing cholangitis, anatomic abnormalities, infection

Clinical Issues

- Elevated bilirubin and alkaline phosphatase very common
  - Patients often present with abdominal pain, jaundice
  - Jaundice variably present depending on severity of obstruction
- Treatment and prognosis depend on underlying cause of obstruction

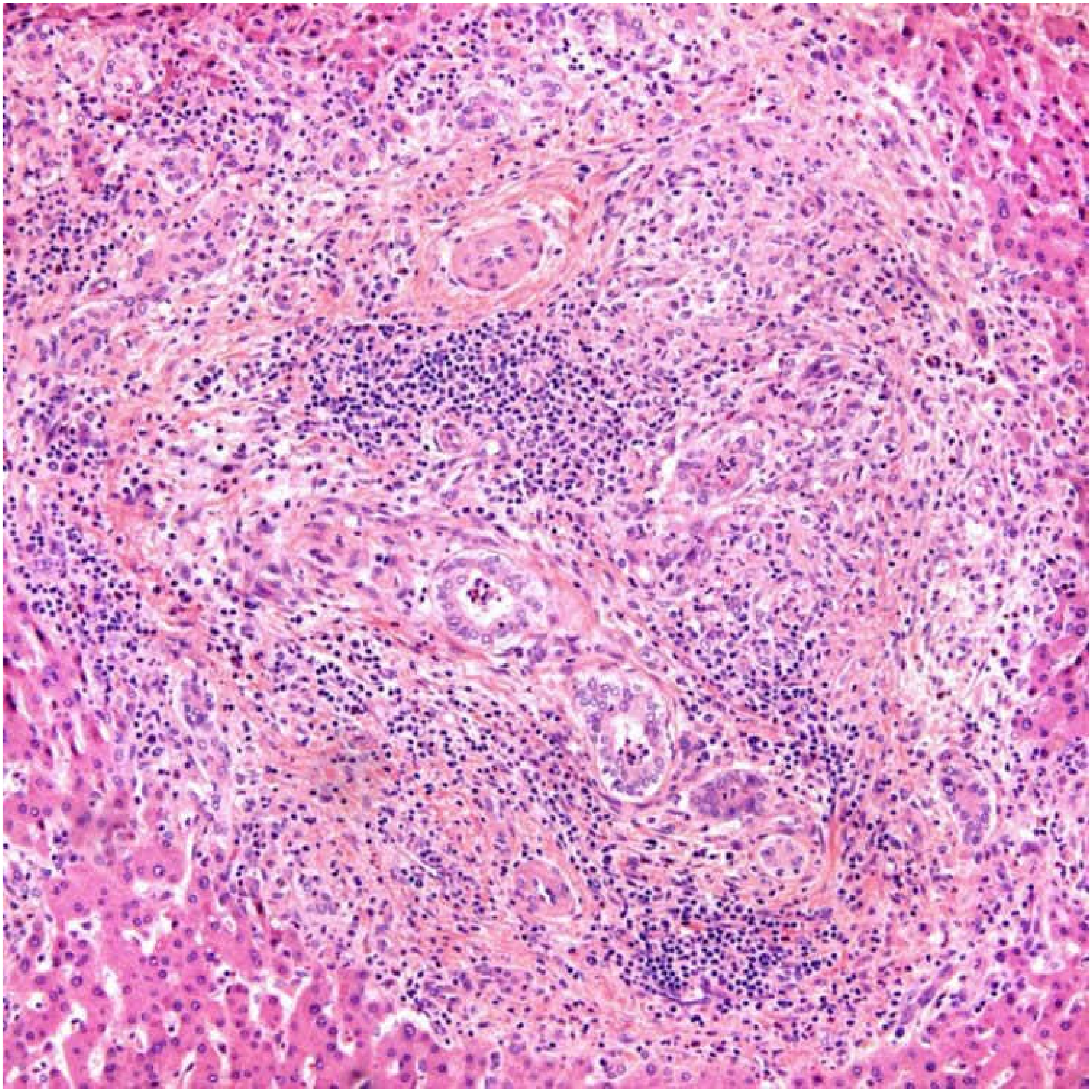
Imaging

- Cholangiography is invasive, but allows direct visualization of duct lumen, defines site, and often reveals cause of obstruction

Microscopic

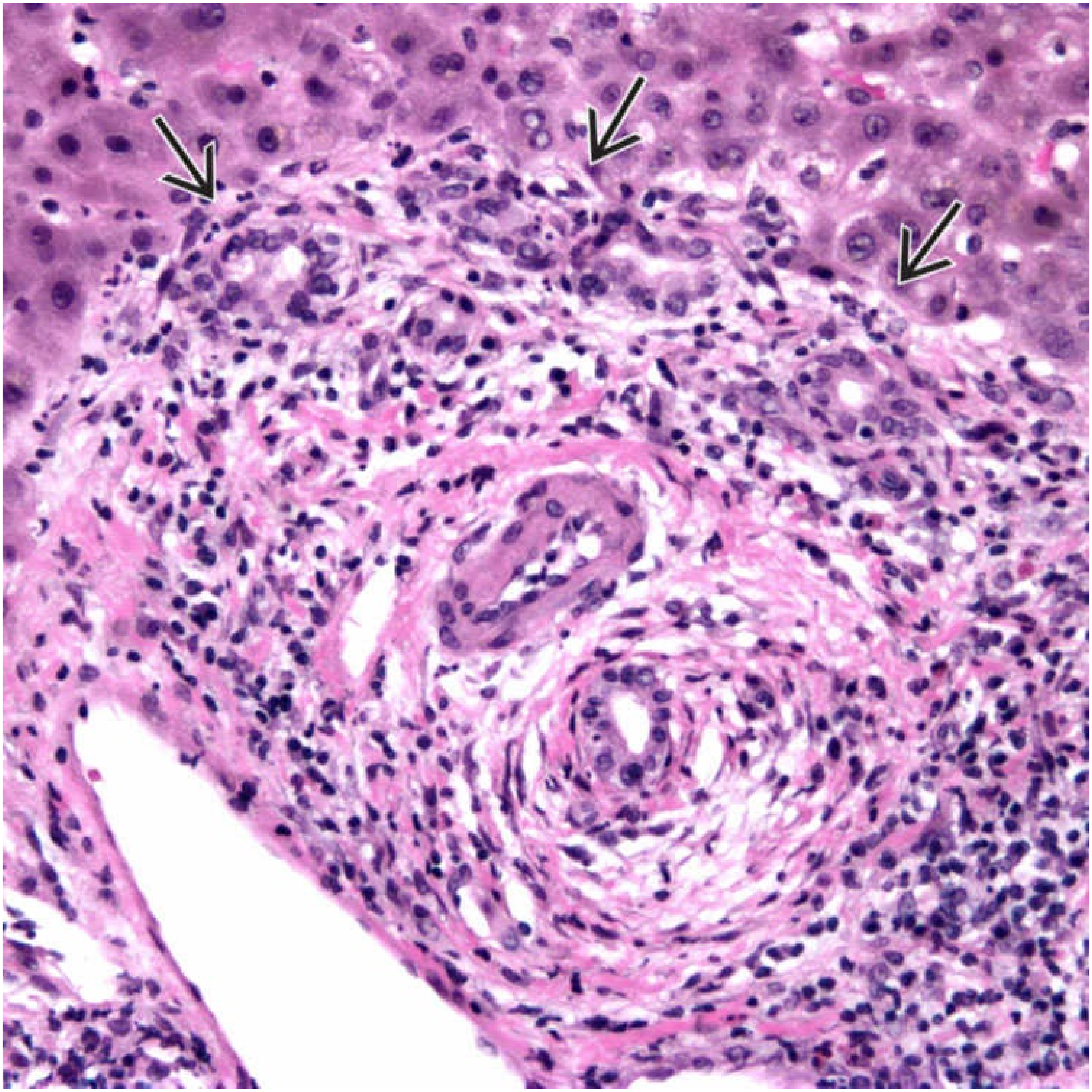
- Histologic findings nonspecific, affected by duration, severity, and cause of LBDO
  - Portal edema, mixed inflammation, ductular reaction
    – Neutrophils often prominent
- Reactive epithelial changes in interlobular bile ducts ± neutrophils

- Canalicular cholestasis typically earliest change
– May be absent if blockage is partial or intermittent
- Copper deposition, fibrosis and even cirrhosis can develop if process is chronic



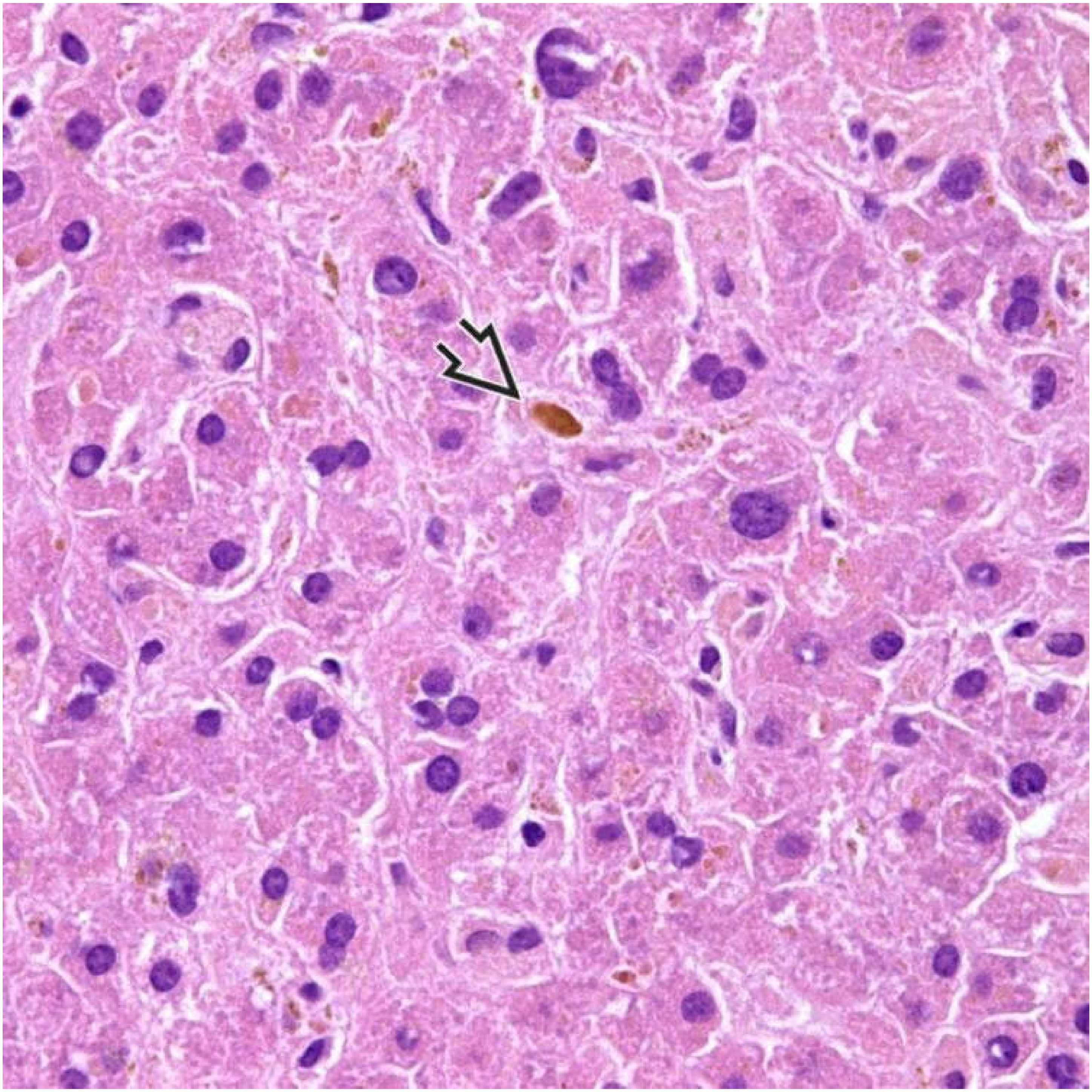
Portal Edema

Portal edema is a common feature of large bile duct obstruction. It appears as expansion and pallor of the portal tracts. Note the mixed portal inflammation, ductular reaction, and neutrophils in the lumen of the interlobular bile duct.



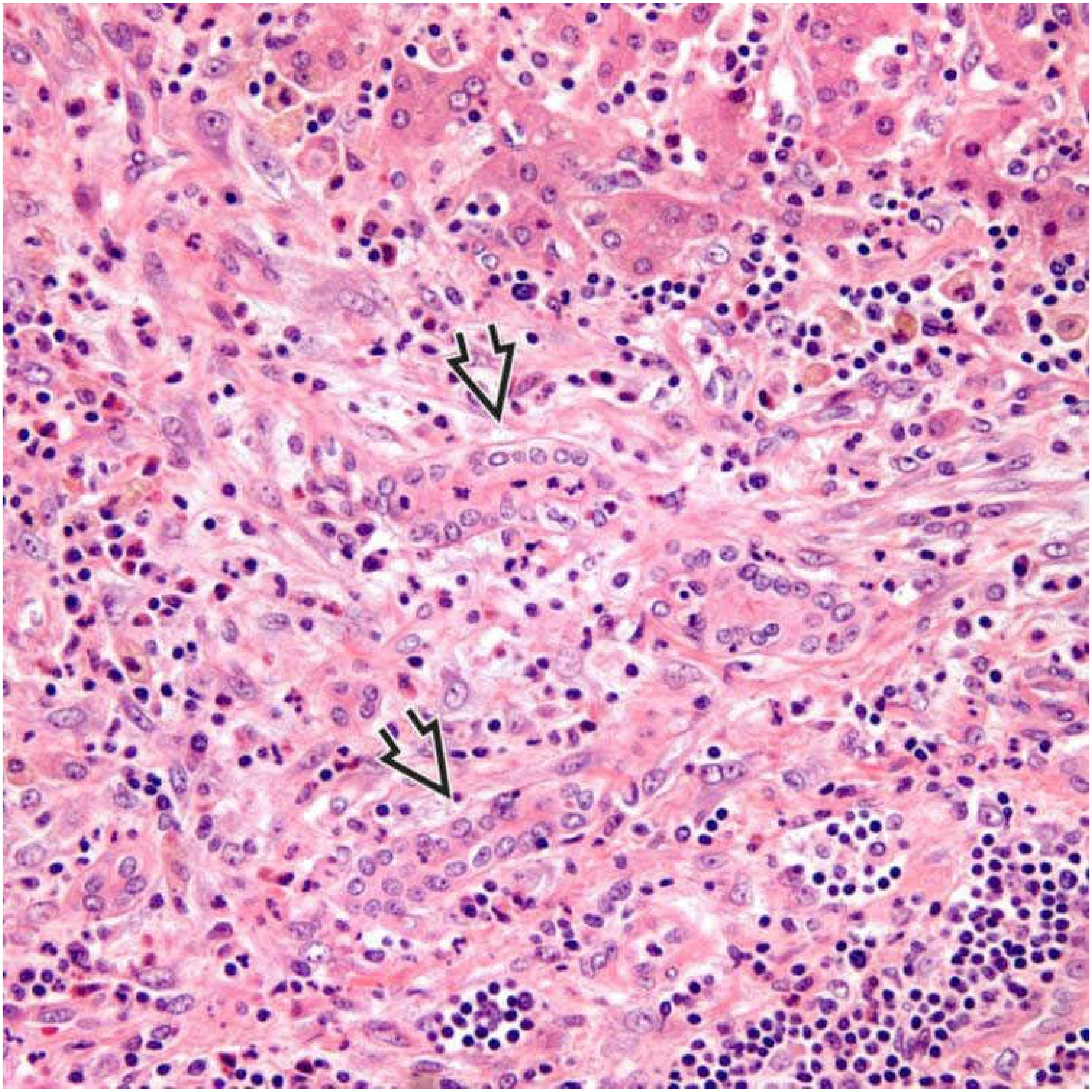
Ductular Reaction

This case of large bile duct obstruction shows marked periductal edema, ductular reaction at the periphery of the portal tracts → with admixed neutrophils, and a mixed portal inflammatory infiltrate.



Canalicular Cholestasis

Canalicular cholestasis, featuring prominent bile plugs throughout the parenchyma ➪, is often the earliest change seen in liver biopsies from patients with large bile duct obstruction.



Mixed Inflammation
This portal tract is edematous, and features mixed inflammation with numerous neutrophils and eosinophils, which is typical of large bile duct obstruction. The neutrophils also infiltrate the bile duct ➩, and are present in the lumen.

TERMINOLOGY

Abbreviations

- Large bile duct obstruction (LBDO)

Definitions

- Mechanical blockage of extrahepatic or large intrahepatic bile ducts

- Changes on liver biopsy are secondary to obstructive biliary process

ETIOLOGY/PATHOGENESIS

Multifactorial

- Gallstones, neoplasms/masses
- Strictures, sclerosing cholangitis (primary or secondary)
- Biliary atresia
- Anatomical abnormalities of biliary tree
- Parasitic infection

CLINICAL ISSUES

Presentation

- Abdominal pain
  - Jaundice (may be absent in partial or low-grade obstruction)
  - Pruritus, steatorrhea
  - Complications
  - Bacterial cholangitis/sepsis
  - Cirrhosis
  - Fat-soluble vitamin deficiencies

Laboratory Tests

- Elevated bilirubin and alkaline phosphatase

Treatment

- Diagnose and treat cause of obstruction

Prognosis

- Depends on underlying cause of LBDO

IMAGING

General Features

- Ultrasound and CT can confirm dilated bile ducts
  - May be absent in early or intermittent obstruction, or if ducts are fibrotic
- Cholangiography is invasive but allows direct visualization of duct lumen, defines site, and often reveals cause of obstruction

MICROSCOPIC

Histologic Features

- Histologic findings nonspecific and affected by duration, severity, and cause of LBDO
  - Portal tract alterations
  - ○ Edema
  - ○ Mixed portal inflammation with prominent neutrophils and variably present eosinophils
  - ○ Ductular reaction at edges of portal tracts
  - – Often with admixed neutrophils

○ Reactive changes in interlobular bile ducts

– Neutrophils may infiltrate ductal epithelium; does not necessarily imply biliary tree infection

- Cholestasis
  - ○ Canalicular cholestasis typically earliest change
    - – Often accompanied by inflammation, hepatocellular injury
    - – May be absent if blockage is partial or intermittent
    - – Hepatocellular cholestasis may also be present
  - ○ Ductal cholestasis rarely seen
  - ○ Bile lakes may form from leakage of bile from ducts/ductules
  - ○ Large &/or periportal bile infarcts imply high-grade obstruction
  - ○ Features of chronic cholestasis
    - – Periportal cholate stasis (swollen, vacuolated hepatocytes) ± Mallory bodies
    - – Copper staining
    - – Expansion of portal areas by fibrosis, inflammation, ductular proliferation
  - ○ Fibrosis
    - – Irregular expansion of portal tract yields portal/portal septa in chronic LBDO
    - – Eventually progresses to biliary cirrhosis if untreated

DIFFERENTIAL DIAGNOSIS

Sepsis

- Ductular reaction with presence of inspissated ductular bile (“ductular cholestasis”)
- Other clinical and laboratory features of infection

Drug-Induced Cholestasis

- History of offending drug; absence of ductular reaction

Total Parenteral Nutrition

- History of use; steatosis often present

Acute Viral Hepatitis

- May have cholestatic features, ductular reaction in addition to other parenchymal changes of viral hepatitis
- Transaminases elevated as well as bilirubin, alkaline phosphatase
- Viral serologic studies helpful

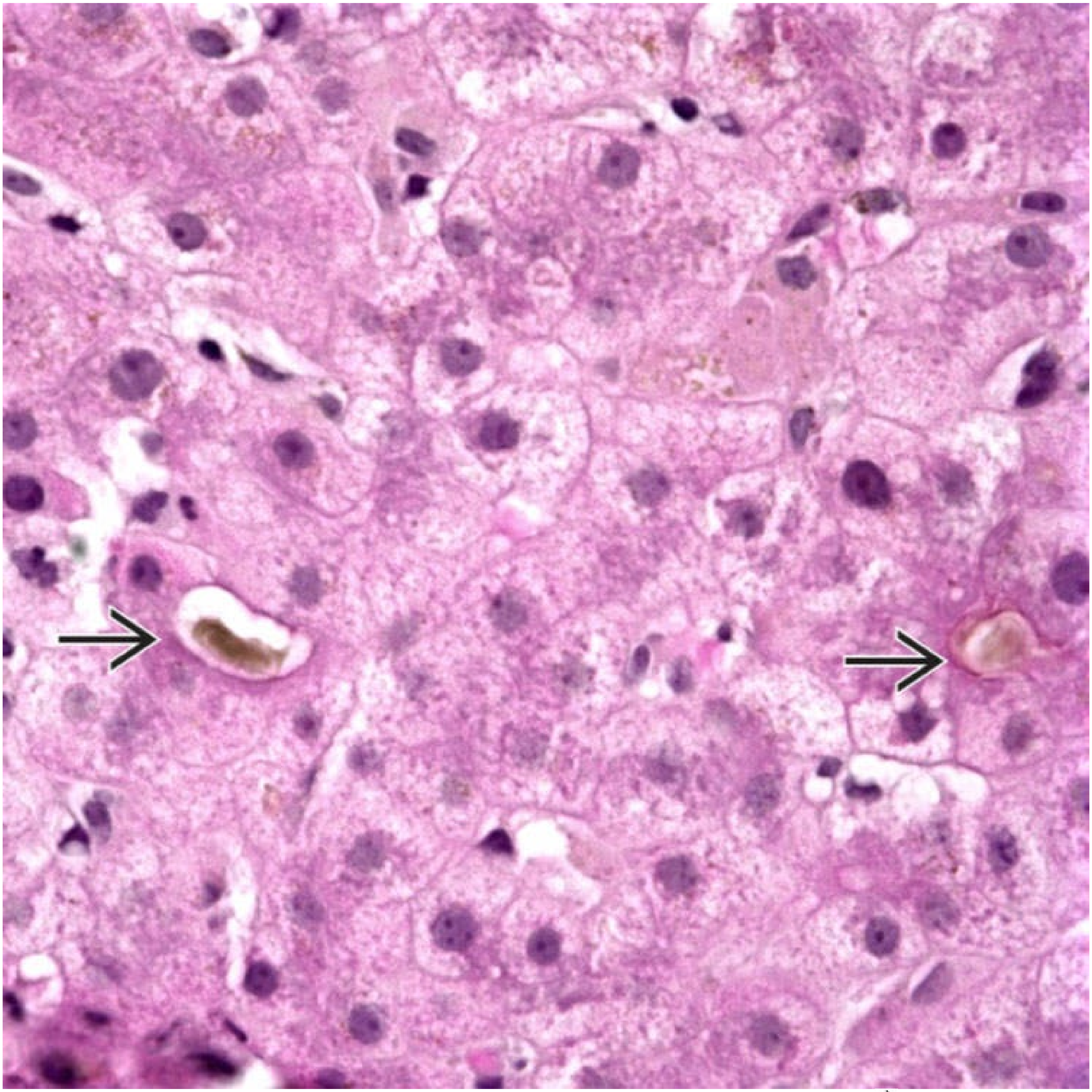
Alcoholic Liver Disease

- Severe disease may feature cholestasis, ductular reaction, reactive bile duct changes
- Look for other features of alcoholic liver disease

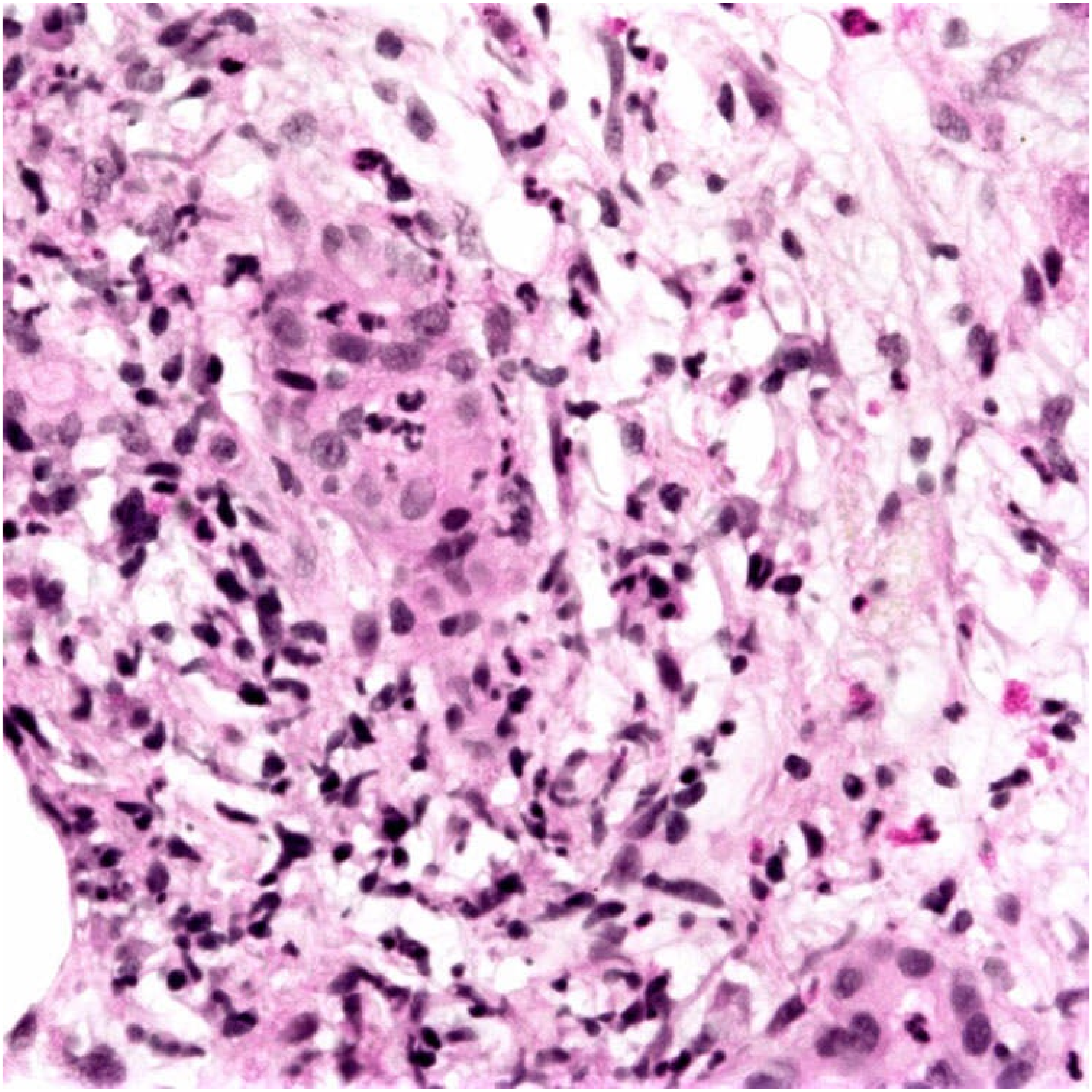
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

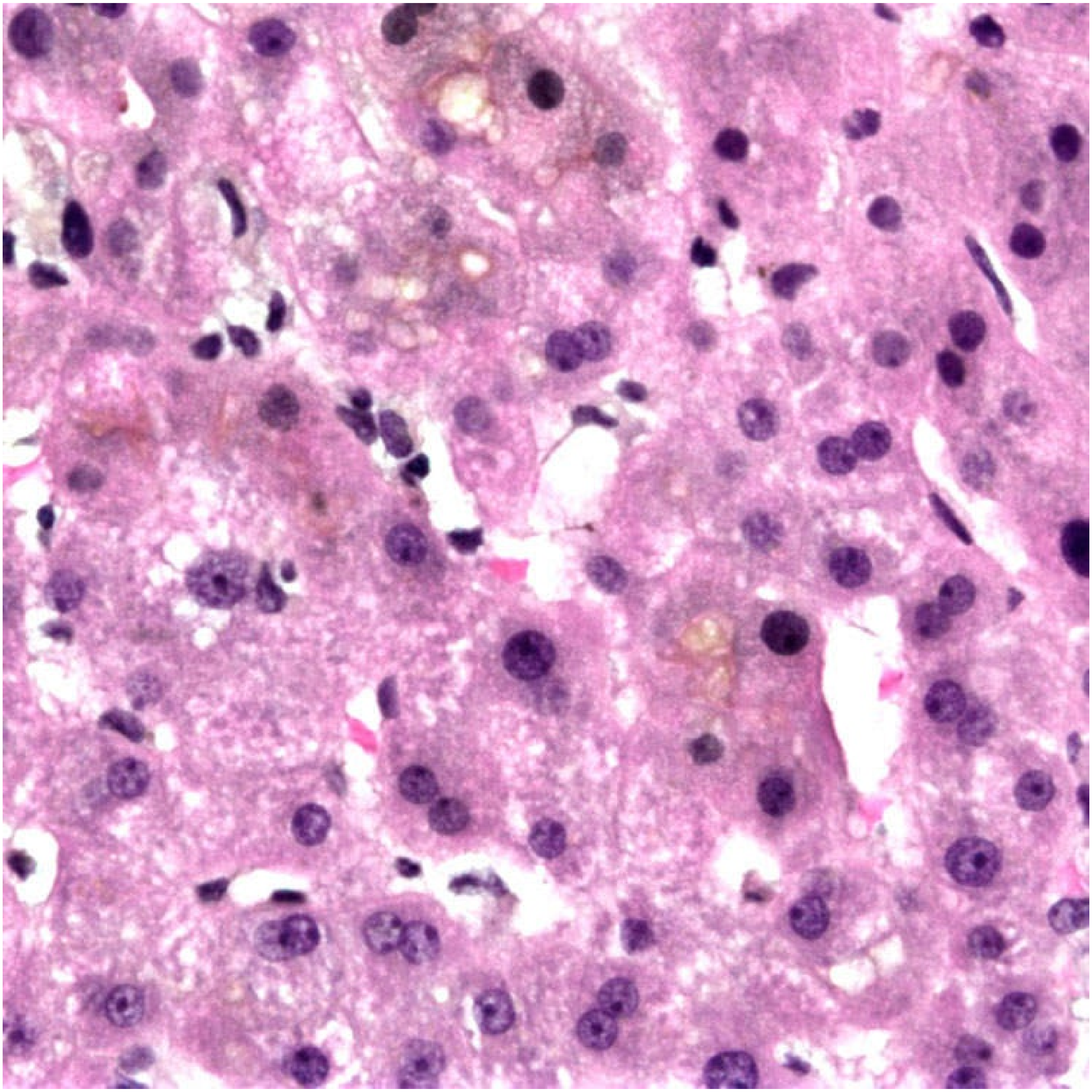
- Usually clinical and radiographic diagnosis
    - Liver biopsy often unnecessary unless clinical findings/radiographic studies equivocal or misleading



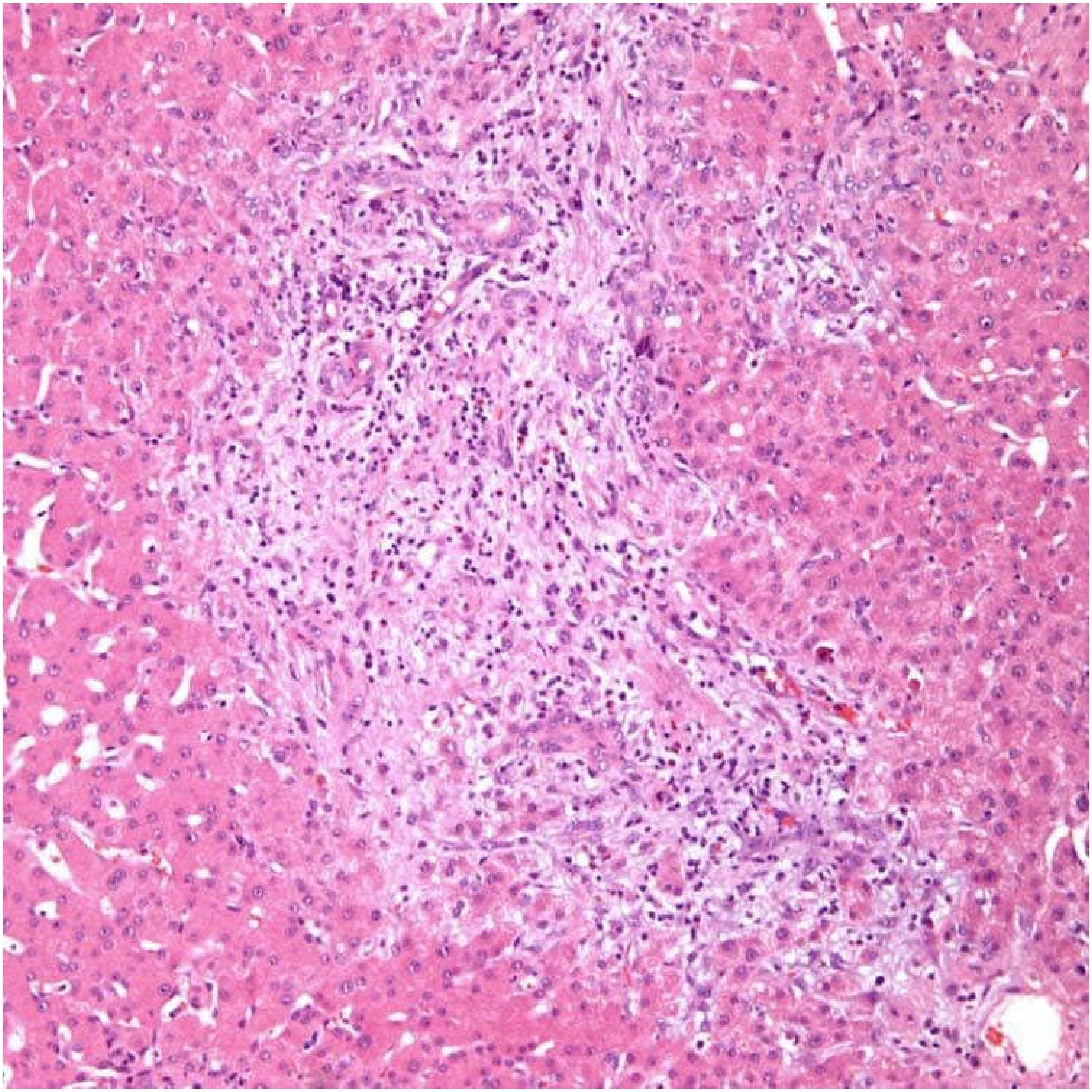
Prominent canalicular bile plugs may be seen in large bile duct obstruction→ .



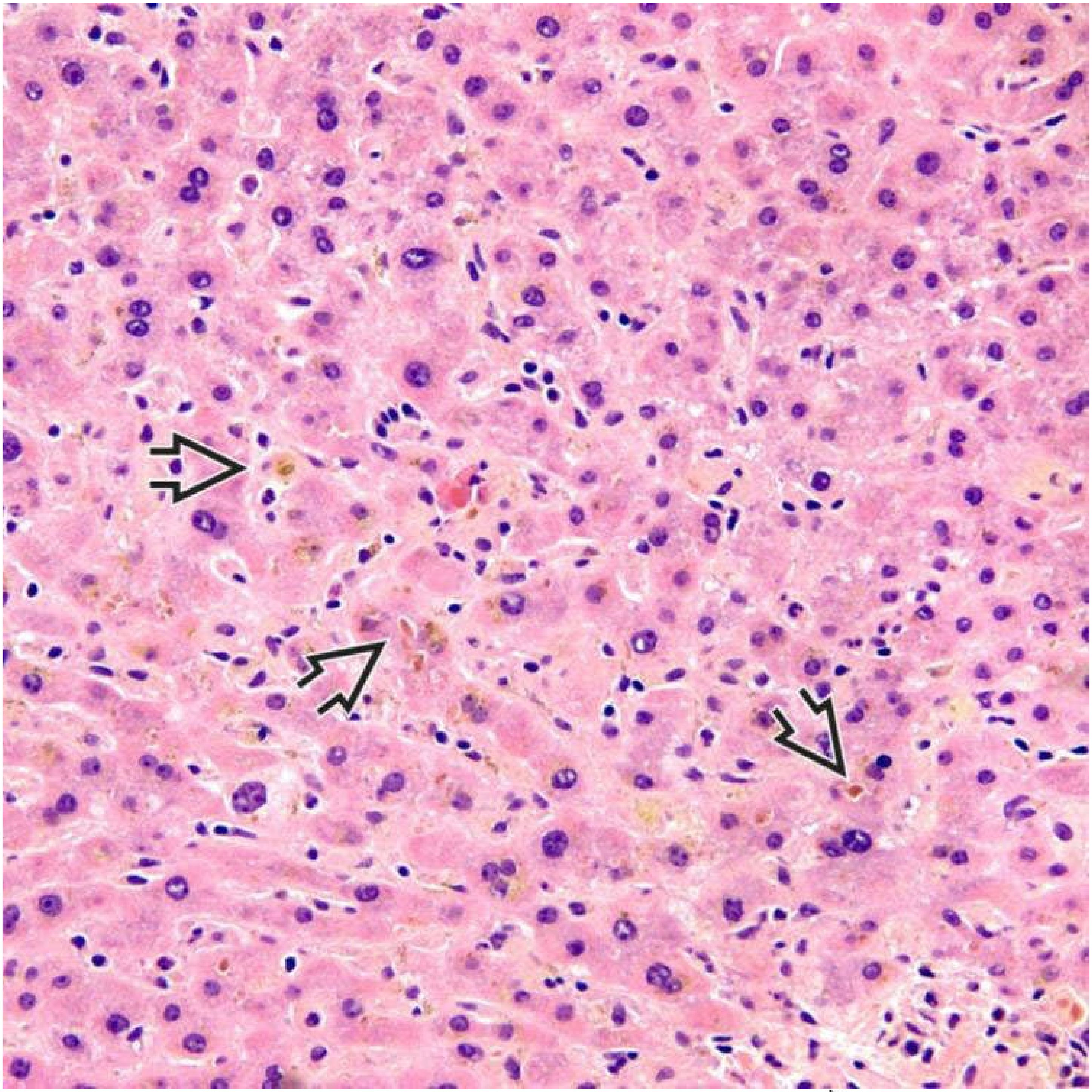
High-power view of a portal tract in large bile duct obstruction shows neutrophilic cholangitis and marked portal edema. Numerous neutrophils and eosinophils are seen within the inflammatory infiltrate.



Cholestasis is often the earliest feature of large bile duct obstruction.



This expanded, edematous portal tract contains mixed inflammation with prominent neutrophils and eosinophils. Ductular reaction is present at the periphery.



Canalicular cholestasis, featuring prominent bile plugs throughout the parenchyma, is often the earliest change seen in liver biopsies from patients with large bile duct obstruction.

SELECTED REFERENCES

1. Lefkowitch, JH. Histological assessment of cholestasis. *Clin Liver Dis*. 2004; 8(1):27–40. [v].
2. Li, MK, et al. The pathology of cholestasis. *Semin Liver Dis*. 2004; 24(1):21–42.
3. Morris, JS, et al. Percutaneous liver biopsy in patients with large bile duct obstruction. *Gastroenterology*. 1975; 68(4 Pt 1):750–754.

4.Christoffersen, P, et al. Histological changes in human liver biopsies following extrahepatic biliary obstruction. *Acta Pathol Microbiol Scand*. 1970; Suppl. 212(Suppl 212):150.

Idiopathic Adulthood Ductopenia

KEY FACTS

Terminology

- Heterogeneous group of cholestatic diseases of unknown etiology in adults characterized by ductopenia

Clinical Issues

- Typically seen in young or middle-aged adults
  - Jaundice, pruritus
  - Can be asymptomatic
  - Biochemical evidence of cholestasis
- Normal extrahepatic bile ducts
- Variable prognosis, ranging from benign clinical course to progressive disease requiring liver transplantation

Microscopic

- Loss of interlobular bile ducts in > 50% portal tracts
  - Mild-form idiopathic adulthood ductopenia (IAD) may show duct loss in < 50% of portal tracts
- Mild ductular reaction may be seen
- Usually minimal, if any, nonspecific portal inflammation
- Sequelae of ductopenia
  - Cholestasis, cholate stasis, copper deposition in periportal hepatocytes, biliary fibrosis/cirrhosis

Ancillary Tests

- Cytokeratin 7 or 19 immunostaining can help highlight bile ducts

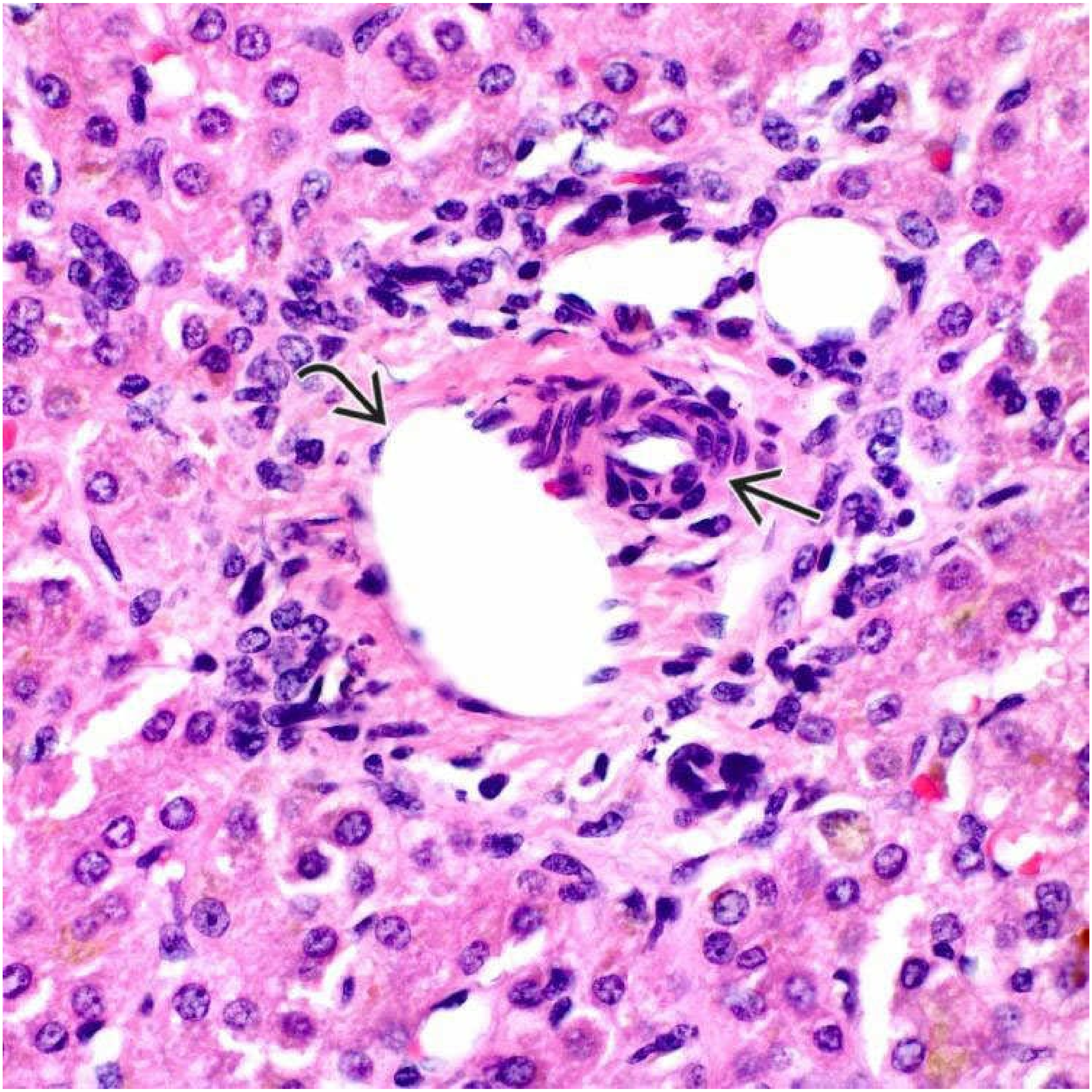
Top Differential Diagnoses

- Primary biliary cholangitis
  - Primary sclerosing cholangitis
  - May be difficult to separate from small duct variant

- Drug-induced vanishing bile duct syndrome
- Hodgkin lymphoma
  - Granuloma, cholestasis, &/or ductopenia can occur whether or not liver is involved by lymphoma

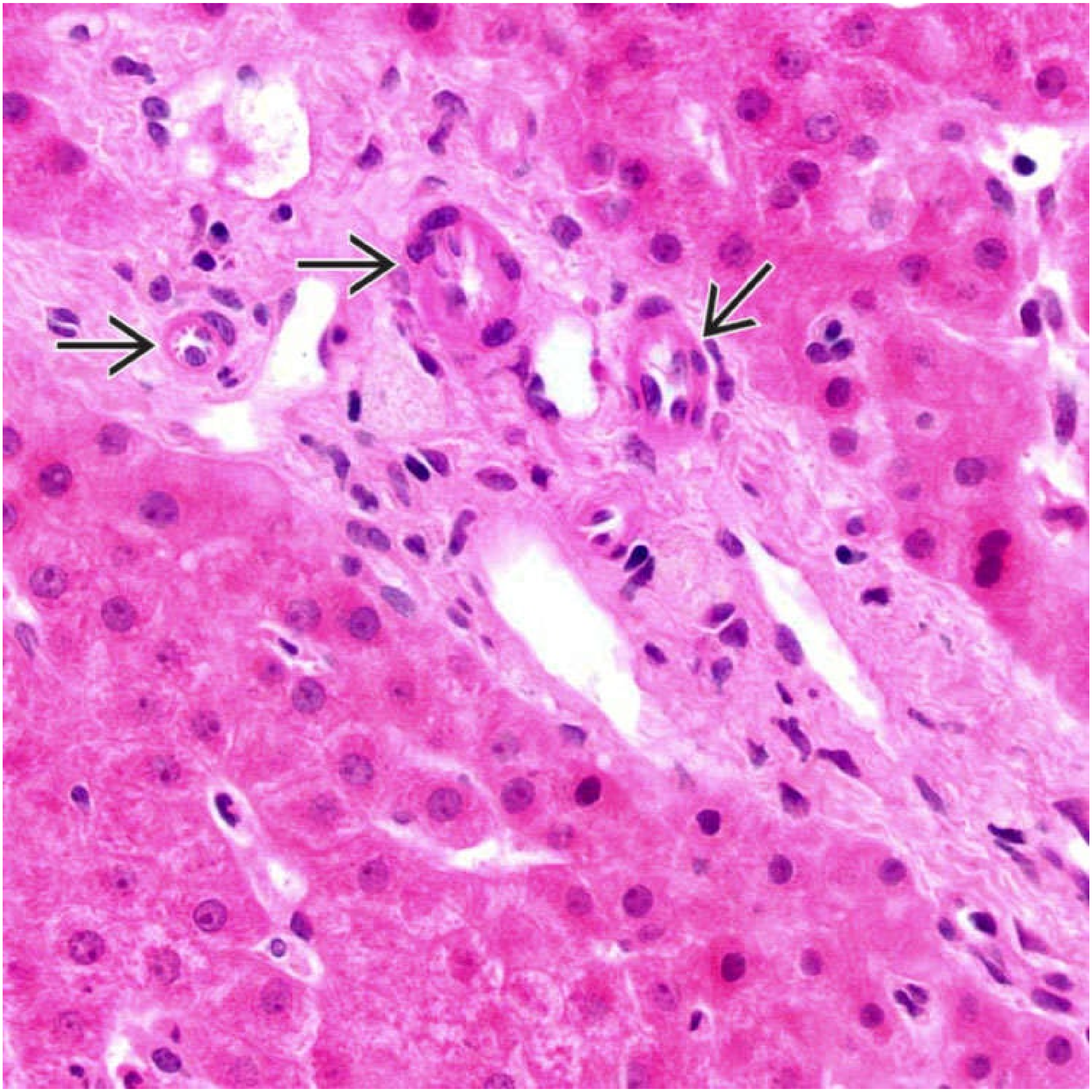
Diagnostic Checklist

- Diagnosis of exclusion

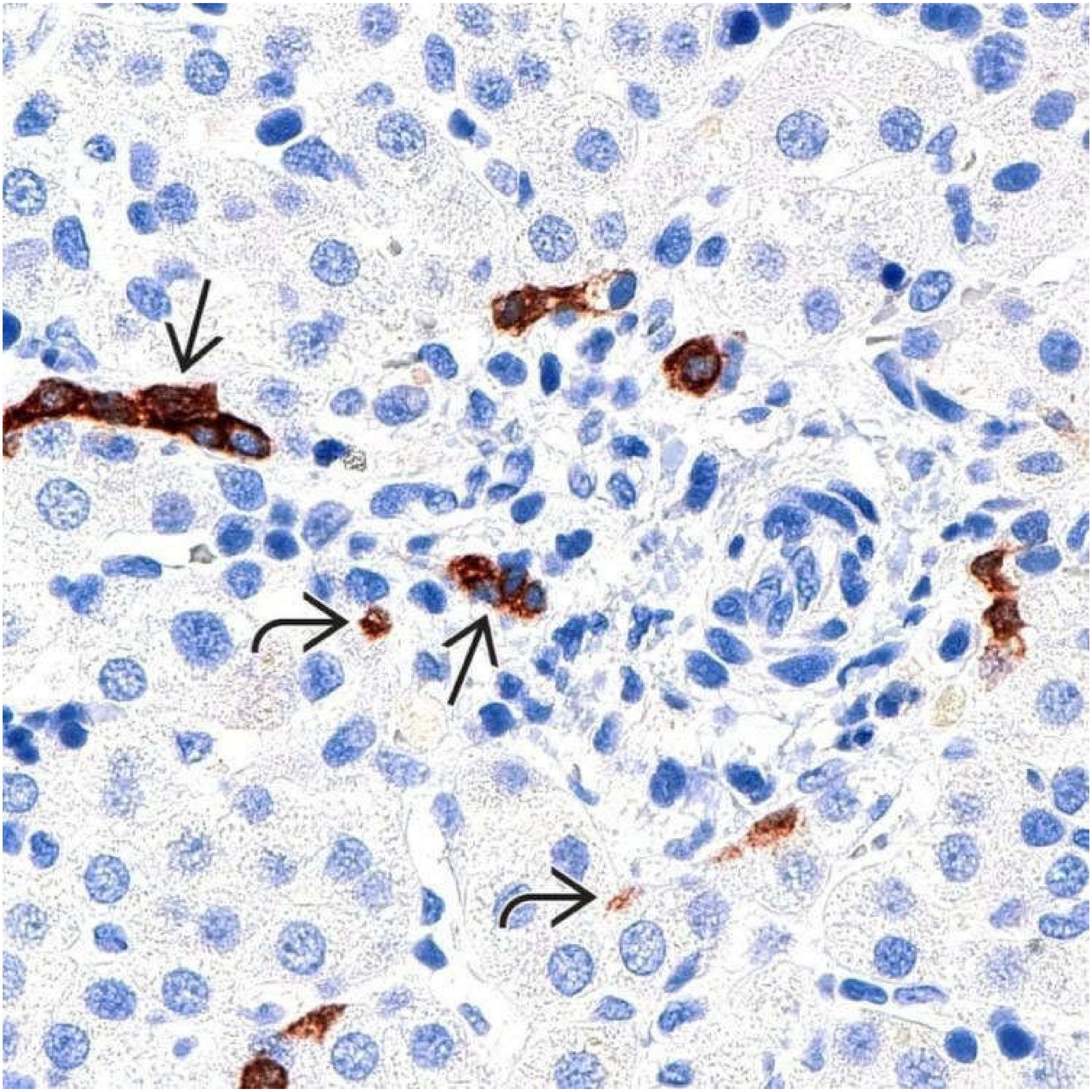


Ductopenia

This liver biopsy from a young man with persistent elevation of serum alkaline phosphatase levels and hyperbilirubinemia with no identifiable cause shows the presence of the hepatic artery → and portal vein ↷ but no bile duct in the majority of portal tracts. Note the presence of minimal portal inflammation.

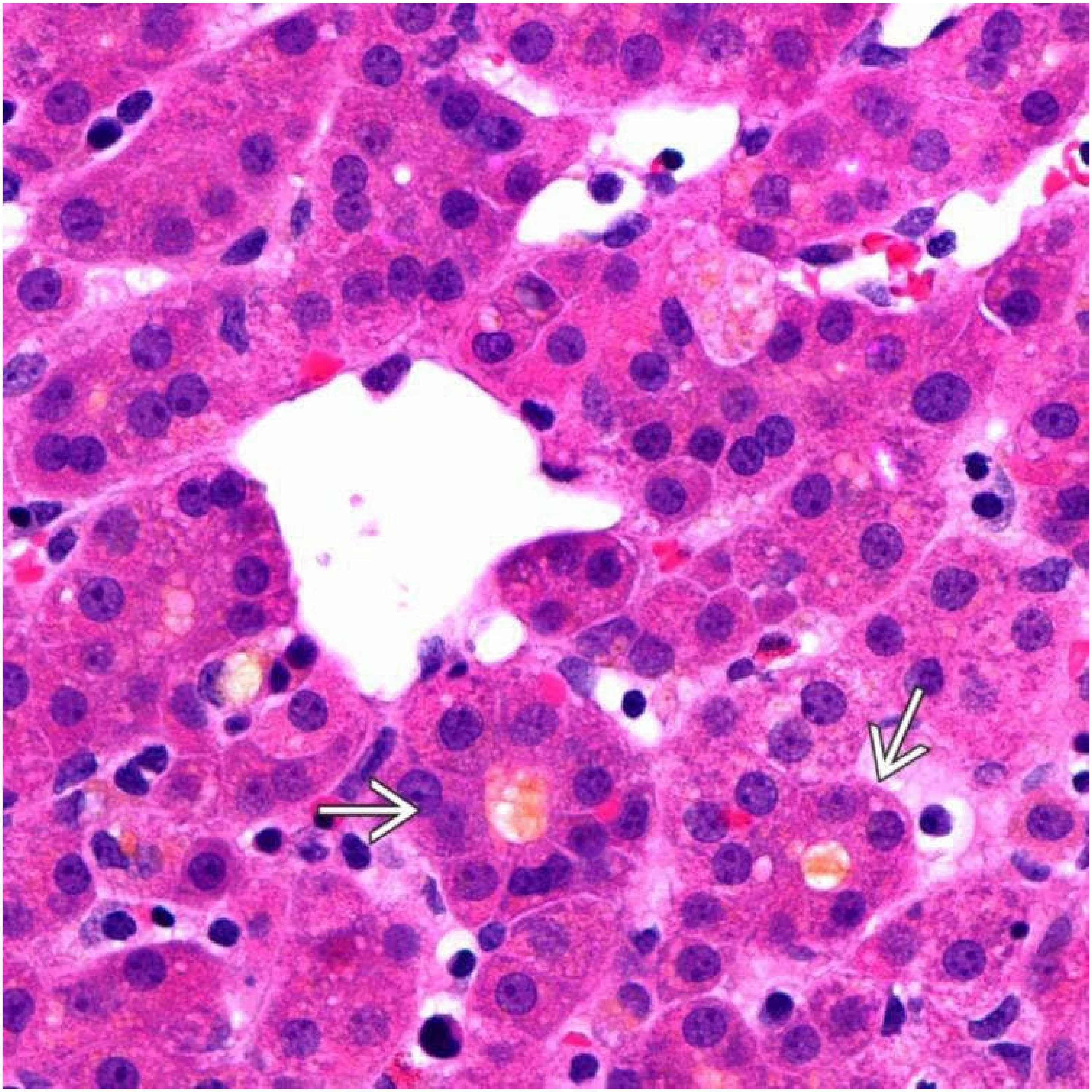


Ductopenia
Another case of idiopathic adulthood ductopenia shows hepatic artery branches → in a portal tract, unaccompanied by bile ducts. Ductular reaction is not evident in this portal tract.



CK7 Immunostaining

This case of idiopathic adulthood ductopenia shows the absence of bile duct as confirmed by CK7 immunostaining. The positively stained cells represent bile ductules → or canals of Hering ↱ .



Cholestasis
This liver biopsy from a patient with idiopathic adulthood ductopenia shows cholestasis with pseudoacinar formation ⇒ indicating a chronic cholestatic process.

TERMINOLOGY

Abbreviations

• Idiopathic adulthood ductopenia (IAD)

Definitions

• Heterogeneous group of cholestatic diseases of unknown etiology in adults characterized by ductopenia

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Late onset of nonsyndromic paucity of intrahepatic bile ducts
- Familial cases may be related to mutations of *ABCB11* (BSEP) or *ABCB4* (MDR3) genes

Infectious Agents

- Postviral duct destruction

Autoimmune Condition

- Small duct primary sclerosing cholangitis in absence of inflammatory bowel disease
- Autoimmune cholangitis in absence of autoantibodies or granuloma

CLINICAL ISSUES

Epidemiology

- Age
  - Typically seen in young or middle-aged adults
- Sex
  - Male predominance

Presentation

- Jaundice, pruritus
  - Can be asymptomatic
  - Biochemical evidence of cholestasis

Laboratory Tests

- Elevated serum alkaline phosphatase, γ-glutamyltransferase, and bilirubin levels

Treatment

- Ursodeoxycholic acid
- Liver transplantation

Prognosis

- Variable, ranging from benign clinical course to progressive disease requiring liver transplantation

IMAGING

Cholangiogram

- Normal extrahepatic bile ducts

MICROSCOPIC

Histologic Features

- Loss of interlobular bile ducts in > 50% portal tracts
  - Up to 25% of normal portal tracts may lack duct
  - Requires at least 10 portal tracts, preferably 20, for evaluation, but diagnosis can be suggested on fewer portal tracts
  - Mild-form IAD may show duct loss in < 50% of portal tracts
- Usually minimal, if any, nonspecific portal inflammation
- Remaining ducts may show features of injury
  - No features of granulomatous cholangiopathy, florid duct lesion, or periduct concentric fibrosis
- Mild ductular reaction may be seen
  - Must be distinguished from bile duct
    - Present at edge of portal tracts near limiting plates
    - Does not travel with hepatic artery
- Sequelae of ductopenia
  - Cholestasis, cholate stasis, copper deposition in periportal hepatocytes, biliary fibrosis/cirrhosis

ANCILLARY TESTS

Immunohistochemistry

- Cytokeratin 7 or 19 can help highlight bile ducts

DIFFERENTIAL DIAGNOSIS

Primary Biliary Cholangitis

- Positive antimitochondrial &/or antinuclear antibodies
- Florid duct lesion, granulomatous cholangiopathy

Primary Sclerosing Cholangitis

- Abnormal cholangiogram
- Association with inflammatory bowel disease
- “Onion skin” periduct concentric fibrosis
- May be difficult to separate from small duct variant

Sarcoidosis

- Large epithelioid granulomas extrahepatic sarcoidosis, elevated angiotensin converting enzyme
- Presence of extrahepatic disease
- Elevated serum angiotensin converting enzyme levels

Cystic Fibrosis

- Focal biliary fibrosis/cirrhosis
- Inspissated eosinophilic concretions in dilated ductules

Cholestatic Drug Reaction

- May cause vanishing bile duct syndrome
  - Ibuprofen, carbamazepine, chlorpromazine, antibiotics, such as amoxicillin-clavulanate, etc.

Hodgkin Lymphoma

- Granuloma, cholestasis, &/or ductopenia can occur whether or not liver is involved by lymphoma

Ischemic Cholangiopathy

- History of injury to hepatic artery

Chronic Graft-vs.-Host Disease

- History of bone marrow or stem cell transplantation

Chronic Allograft Rejection

- History of liver transplantation
- Foam cell arteriopathy

Langerhans Cell Histiocytosis

- Infiltration of liver and bile ducts by Langerhans dendritic cells expressing CD1a and langerin

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Diagnosis of exclusion

SELECTED REFERENCES

1. Bilal, M, et al. Idiopathic adulthood ductopenia: ‘it is out there’. *Case Rep Gastroenterol*. 2016; 10(1):95–98.

2. Domínguez-Antonaya, M, et al. Idiopathic adulthood ductopenia: a diagnosis: two clinicopathologic courses. *J Clin Gastroenterol*. 2000; 30(2):210–212.

SECTION 4
PEDIATRIC CHOLESTATIC DISORDERS

OUTLINE

Biliary Atresia

KEY FACTS

Terminology

- Idiopathic necroinflammatory fibrosing process of both extrahepatic and intrahepatic bile ducts
  - 1:5,000 to 1:19,000 newborns

Clinical Issues

- Most common cause of pathologic infant jaundice
  - Conjugated hyperbilirubinemia
  - Neonatal jaundice
  - Dark urine and pale stools
  - Hepatomegaly
- Associated extrahepatic congenital anomalies present in up to 20% of cases
- Surgical intervention required
  - Kasai procedure to reestablish bile flow; best outcome if performed before 45-60 days of age
  - Most frequent indication for pediatric liver transplantation

Macroscopic

- Level of extrahepatic duct obliteration is most common within portal hepatis
- Associated with hypoplastic or atretic gallbladder

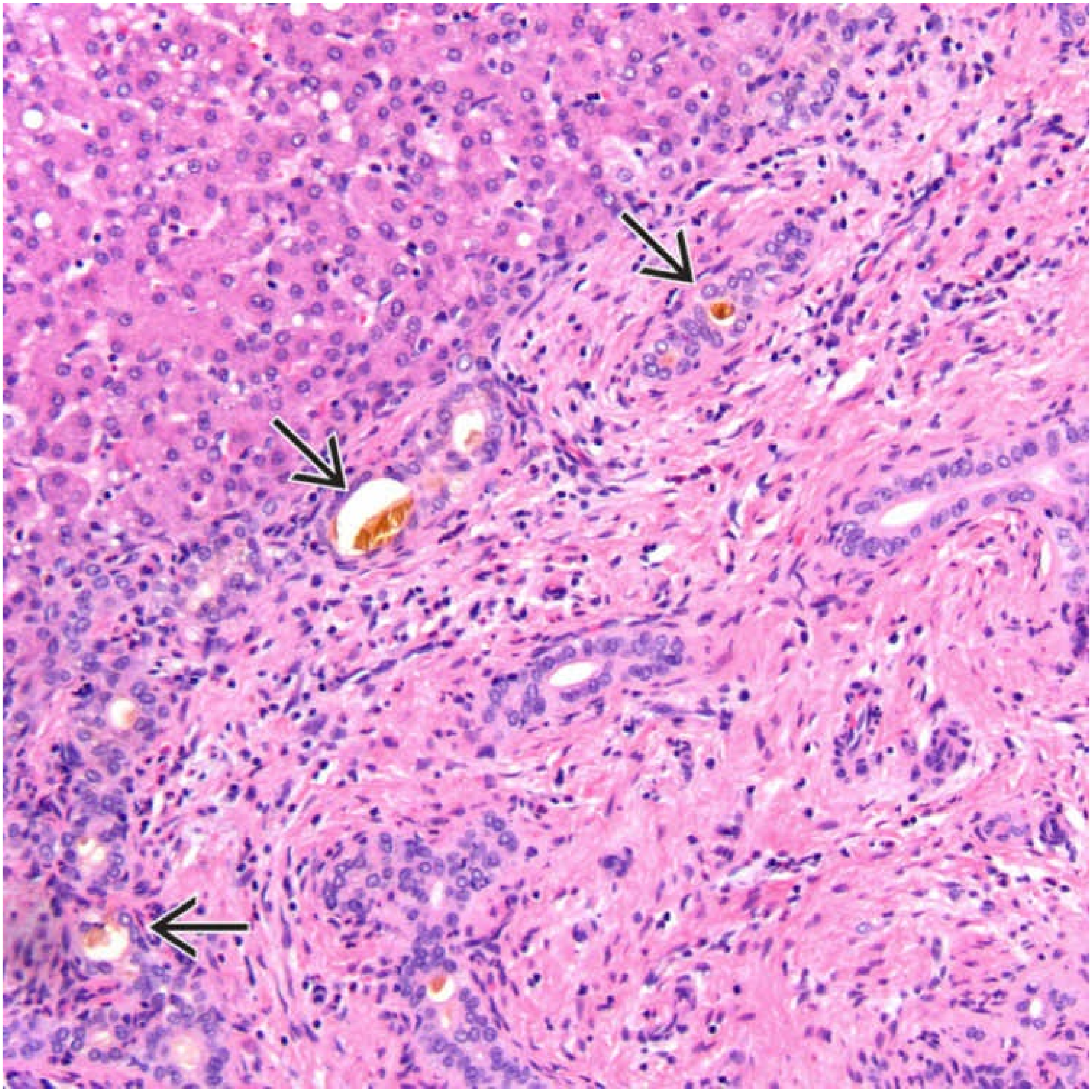
Microscopic

- Ductular reaction, duct/ductular bile plugs, and portal and periportal fibrosis
- Associated with lobular cholestasis, focal giant cell transformation, and extramedullary hematopoiesis
- Careful clinical and radiographic correlation required to exclude other entities in differential diagnosis

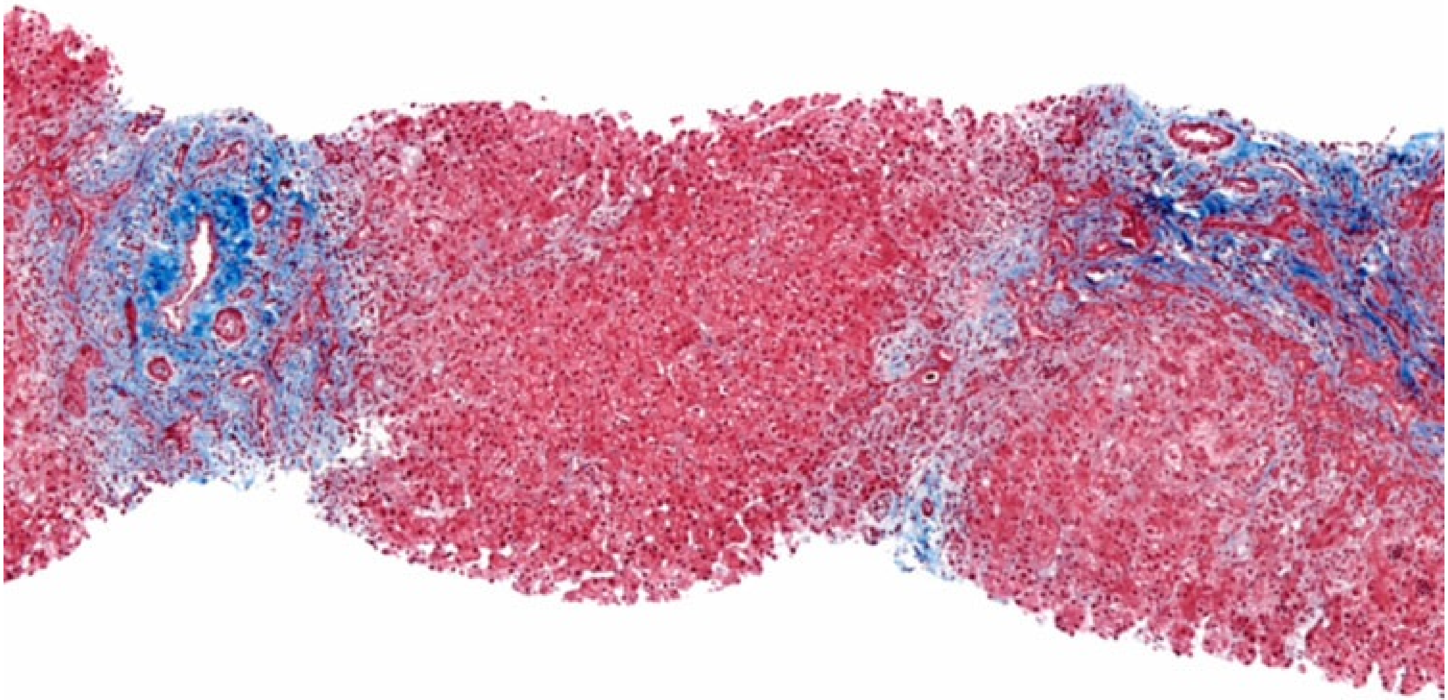
Top Differential Diagnoses

- Idiopathic neonatal hepatitis

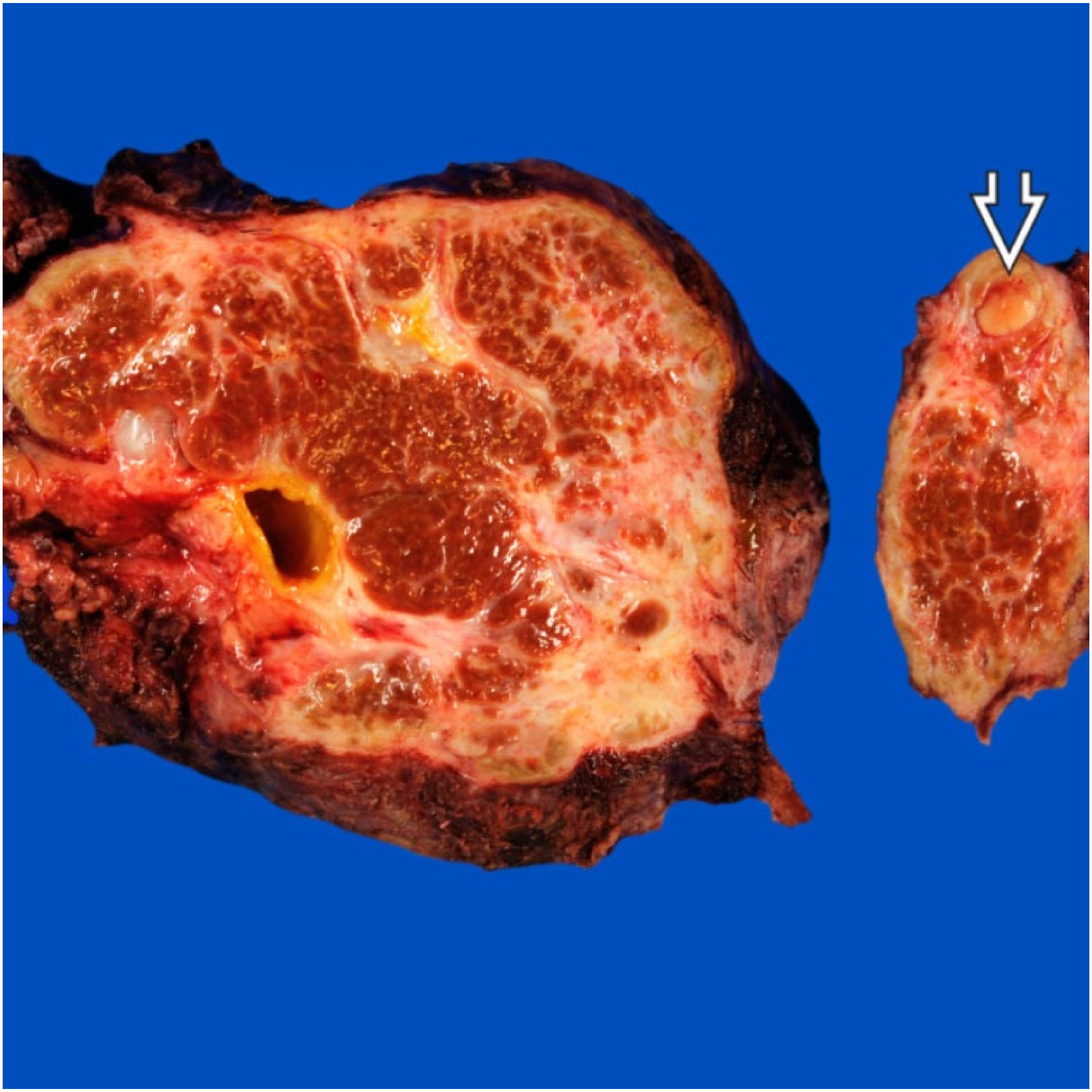
• α-1-antitrypsin deficiency
• Total parenteral nutrition-associated cholestasis
• CMV infection
• Choledochal cyst



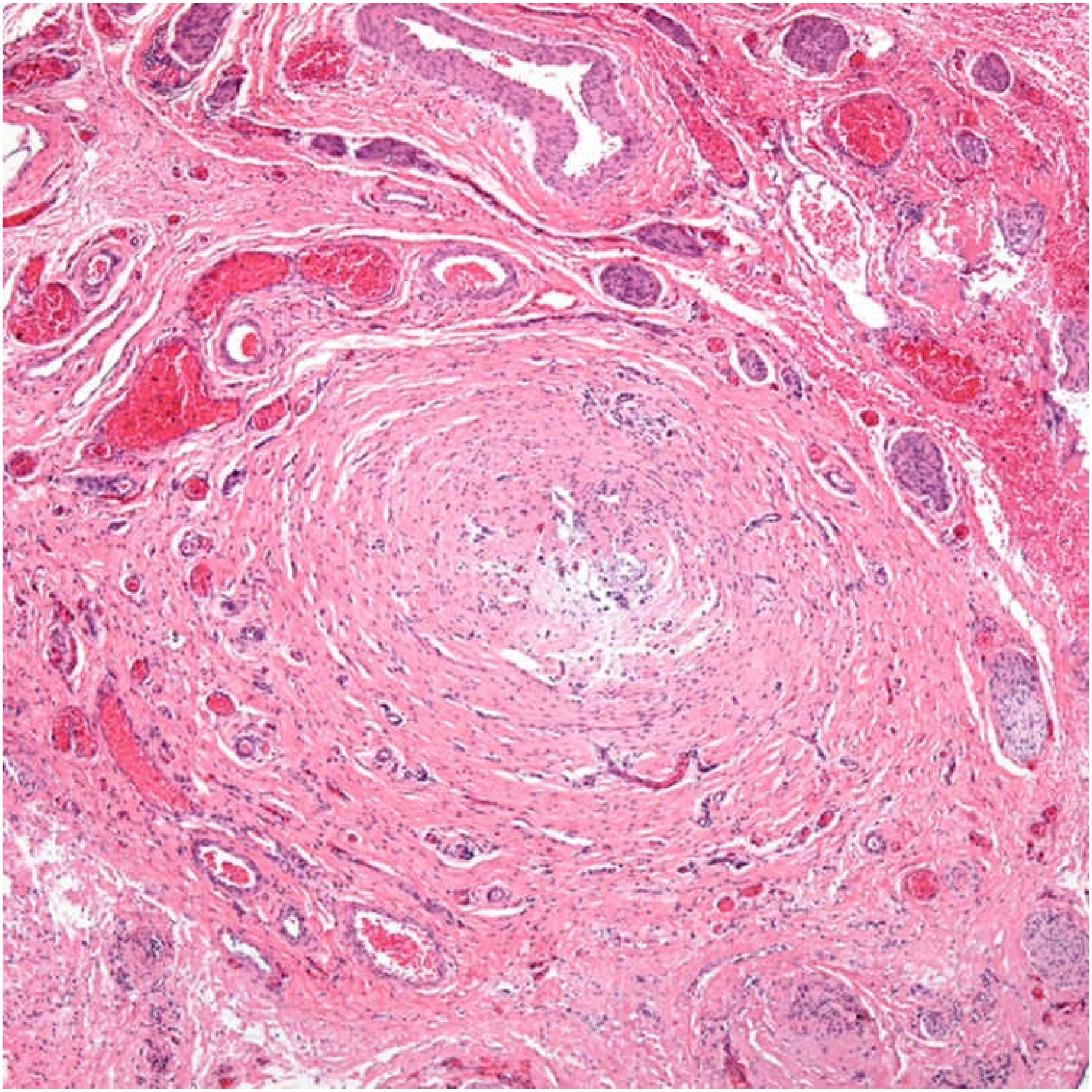
Portal Expansion and Ductular Reaction
Wedge liver biopsy specimen from an 8-week-old infant shows an expanded portal tract with ductular reaction. The ductules along the periphery contain bile plugs →.



Portal Expansion
Trichrome stain highlights the expanded portal tracts with associated ductular reaction in a liver biopsy specimen from a 7-week-old infant.



Gross Appearance
Explanted liver from a 12 year old with biliary atresia (BA) is cirrhotic. In the left lobe of the liver, a 0.9-cm yellow nodule was discovered. Histologically, this was a well-differentiated hepatocellular carcinoma.



Biliary Remnant
Section of biliary remnant removed during Kasai procedure demonstrates a markedly narrowed bile duct-like structure with a nearly absent lumen surrounded by fibrosis. Distal to this section, a patent bile duct lumen was identified.

TERMINOLOGY

Abbreviations

- Biliary atresia (BA)

Synonyms

- Extrahepatic biliary atresia

- ○ Involves both extrahepatic and intrahepatic biliary tree
- – Thus, best classified simply as BA

Definitions

- Idiopathic fibroinflammatory process that destroys bile ducts
    - ○ May culminate in ductopenia and biliary cirrhosis

ETIOLOGY/PATHOGENESIS

Idiopathic

- Probable multiple disease mechanisms
    - ○ Possible roles for viral infection, genetic factors, congenital malformations
    - ○ Associated genetic/chromosomal abnormalities
    - – Trisomy 18 and 21
    - – Cateye and Kabuki syndromes

CLINICAL ISSUES

Epidemiology

- Incidence
    - ○ 1:5,000 to 1:19,000 newborns
    - ○ Most common in East Asian countries

Presentation

- Most common cause of pathologic infant jaundice
    - Clinical triad
    - ○ Persistent neonatal jaundice, beyond 2 weeks of life
    - ○ Dark urine and acholic pale stools
    - ○ Hepatomegaly
- Associated extrahepatic congenital anomalies present in up to 20% of cases
    - ○ Most common is biliary atresia splenic malformation syndrome
- 2 general clinical patterns
    - ○ Prenatal, embryonal/fetal, congenital, or early form
        - – 15-35% of cases
        - – Low birth weight, jaundice at birth
    - ○ Perinatal, postnatal, infantile, acquired, or late form
        - – 65-85% of cases
        - – Healthy anicteric, average-weight neonates
        - – Jaundice usually presents after 2 weeks of age

Laboratory Tests

- Similar to other forms of neonatal cholestasis
  - Conjugated hyperbilirubinemia
  - Variably elevated alkaline phosphatase
  - Variably elevated transaminases
  - γ-glutamyl transpeptidase typically > 200 U/L

Treatment

- Surgery
  - Hepatoportoenterostomy (Kasai procedure)
  - – Palliative procedure to reestablish some bile flow
  - – Best if performed before 45-60 days of age
- Liver transplantation
- – Biliary atresia most frequent indication for pediatric liver transplantation
- – For infants without bile drainage procedure, transplant within 6 months to 2 years of age

Prognosis

- Fatal by age 2 if untreated
  - Prenatal form has worse outcome than postnatal form
- 25-35% of patients with Kasai survive > 10 years without liver transplantation
- 1/3 of patients develop complications of cirrhosis and require transplantation before age 10
- Native cirrhotic liver at risk for malignancy
  - Hepatocellular carcinoma, hepatoblastoma, cholangiocarcinomas
- Good long-term survival after orthotopic liver transplantation
  - Overall patient survival rates at 10 years: 82%
  - Overall graft survival rates at 10 years: 71%
  - Most common abnormal histology shows chronic rejection and centrilobular fibrosis

IMAGING

Radiographic Findings

- Ultrasound
  - Absent or abnormal gallbladder
- Hepatobiliary scan demonstrates failure of excretion of radiotracer into duodenum
  - Nonspecific; other etiologic causes result in false-positive scans
  - Excretion excludes diagnosis of biliary atresia
    - – High sensitivity (~ 100%) but specificity of 87%
- Cholangiography to assess morphology and patency of biliary tree
  - Endoscopic retrograde cholangiopancreatography
    - – Invasive procedure, requires general anesthesia and is technically difficult
  - Intraoperative cholangiogram

MACROSCOPIC

Surgical Classification

- Based on level of extrahepatic duct obliteration
  - Type I (5-10%)
    - Within common bile duct
    - If gallbladder present, likely contains bile
  - Type II (3-5%)
    - Within common hepatic duct
    - If gallbladder present, does not contain bile
  - Type III (> 85-90%)
    - Within portal hepatis
    - Hypoplastic or atretic gallbladder

MICROSCOPIC

Histologic Features

- Obstructive-type pattern of injury
  - Nonspecific
  - Clinical correlation required to exclude other entities in differential diagnosis
- Should have at least 5-7 evaluable portal tracts on biopsy
  - Expanded portal tracts with edema, inflammation, ductular reaction
  - Bile plugs within ducts/ductules
  - Periportal and bridging fibrosis with eventual biliary cirrhosis
  - Bile duct loss and ductopenia can develop
- Lobular features
  - Canalicular cholestasis with variable pseudoacinar transformation
  - Focal giant cell transformation
  - Scattered foci of extramedullary hematopoiesis
- Histologic stages of biliary atresia in patients who have not undergone surgery; timing of stages only approximation
  - Early stage: 1-4 weeks
    - Nonspecific, features not diagnostic
    - Cholestasis with minimal inflammation
    - Few lobular multinucleated hepatocytes (giant cell transformation)
  - 2nd stage: 4-7 weeks
    - Characteristic obstructive features
    - Ductular reaction, best developed at or after 6 weeks, is most reliable criterion
    - Portal tract edema and variable inflammation
    - Interlobular duct epithelial damage
    - Cholestasis with bile plugs

- 3rd stage: 7-8 weeks
    - Portal and periportal fibrosis
- 4th stage: 10 weeks
    - Portal to bridging fibrosis
    - Inflammation decreases
    - Variable periductal fibrosis
- Last stage: > 12 weeks
    - Biliary cirrhosis
    - Ductular reaction may not be prominent
    - Variable paucity of interlobular bile ducts

- Histologic features of biliary remnant very variable
  - Single-duct or multiple-duct/ductule profiles that may have narrowed lumen
    - Dense fibrosis, granulation-like tissue, or active fibroplasia ± inflammation
    - Squamous metaplasia of ductal epithelium has been described
    - Cartilage rarely seen
  - Some cases show no ductal lumen, just fibrous cord

DIFFERENTIAL DIAGNOSIS

Idiopathic Neonatal Hepatitis

- Primarily lobular process
  - Hepatocyte disarray with giant cell transformation predominates
  - Absent to minimal ductular reaction

Choledochal Cyst or Cholelithiasis

- Radiographic imaging studies needed

Total Parenteral Nutrition-Associated Cholestasis

- History of total parenteral nutrition; not duct-destructive

α-1-Antitrypsin Deficiency

- Decreased levels of serum α-1-antitrypsin, abnormal genotype
- Typical periportal PAS-D(+) cytoplasmic globules may not be evident before 12 weeks of age

Cytomegalovirus Infection

- CMV in endothelial cells, hepatocytes, or bile duct epithelium
  - Important to use immunohistochemistry because inclusions often focal

Alagille Syndrome

- Can mimic BA histologically and radiographically

- Ductular reaction without decreased ducts can occur
- Common bile duct hypoplasia without visualization of intrahepatic biliary tree on cholangiogram
- Absence of decreased interlobular ducts, especially < 6 months of age, does not exclude diagnosis of Alagille
  - CK7 useful in assessing ducts/ductules
- Associated clinical manifestations (cardiopulmonary malformations, etc.) useful in diagnosis

Cholestasis-Associated Sepsis

- Sepsis may cause dilated ductules with bile plugs
- Interlobular bile ducts usually intact and free of injury

Progressive Familial Intrahepatic Cholestasis Type 3

- Mutation of *MDR3*, multidrug resistance protein 3, coded by *ABCB4* gene
- Early in course has expanded portal tracts with ductular reaction

Cystic Fibrosis

- Dilated ductules with luminal amorphous pink secretion
- Mutation in *CFTR*

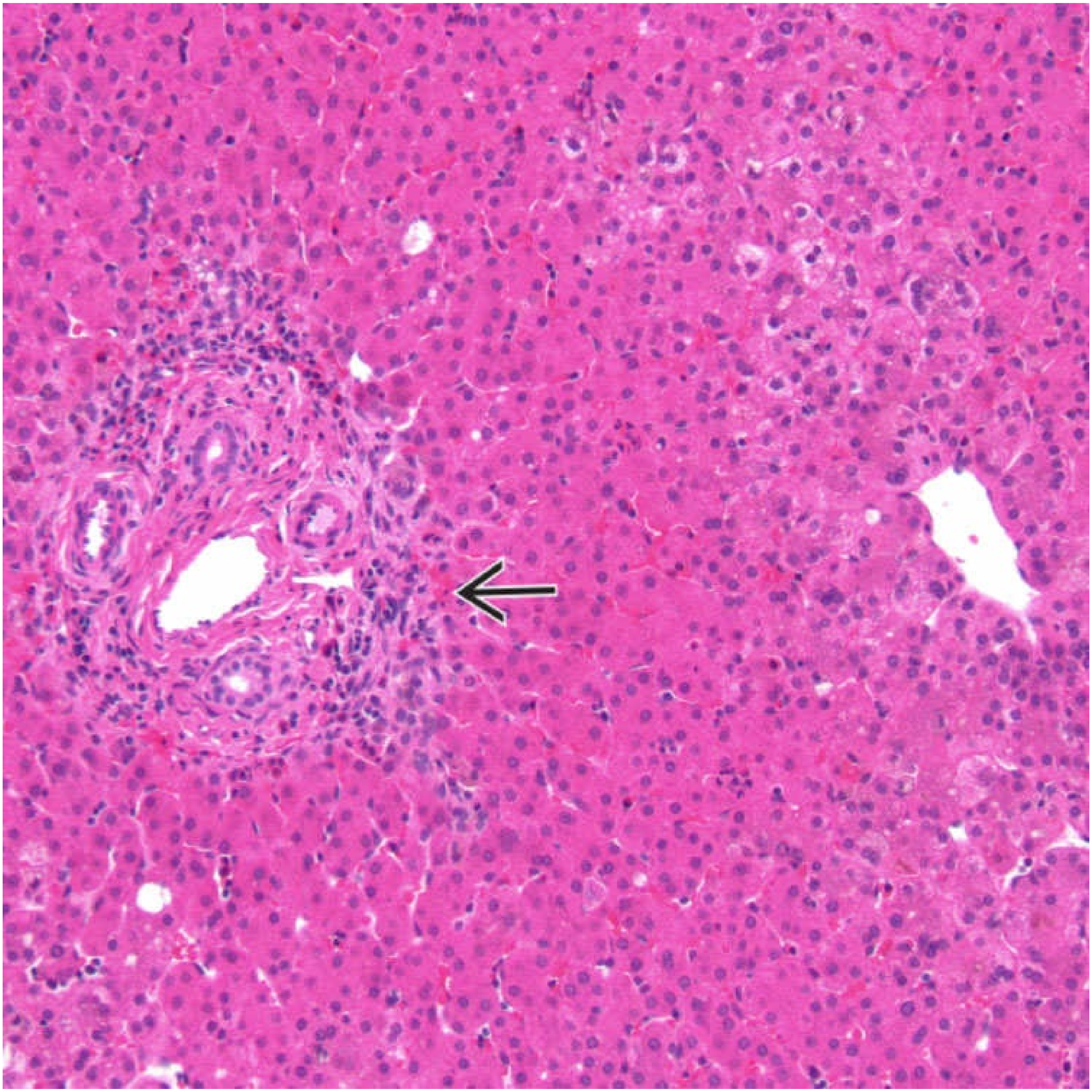
Bile Plug (Inspissated Bile) Syndrome

- Secondary to Rh and ABO group incompatibility, hemolytic disorders, sepsis, cystic fibrosis, dehydration, or total parenteral nutrition

DIAGNOSTIC CHECKLIST

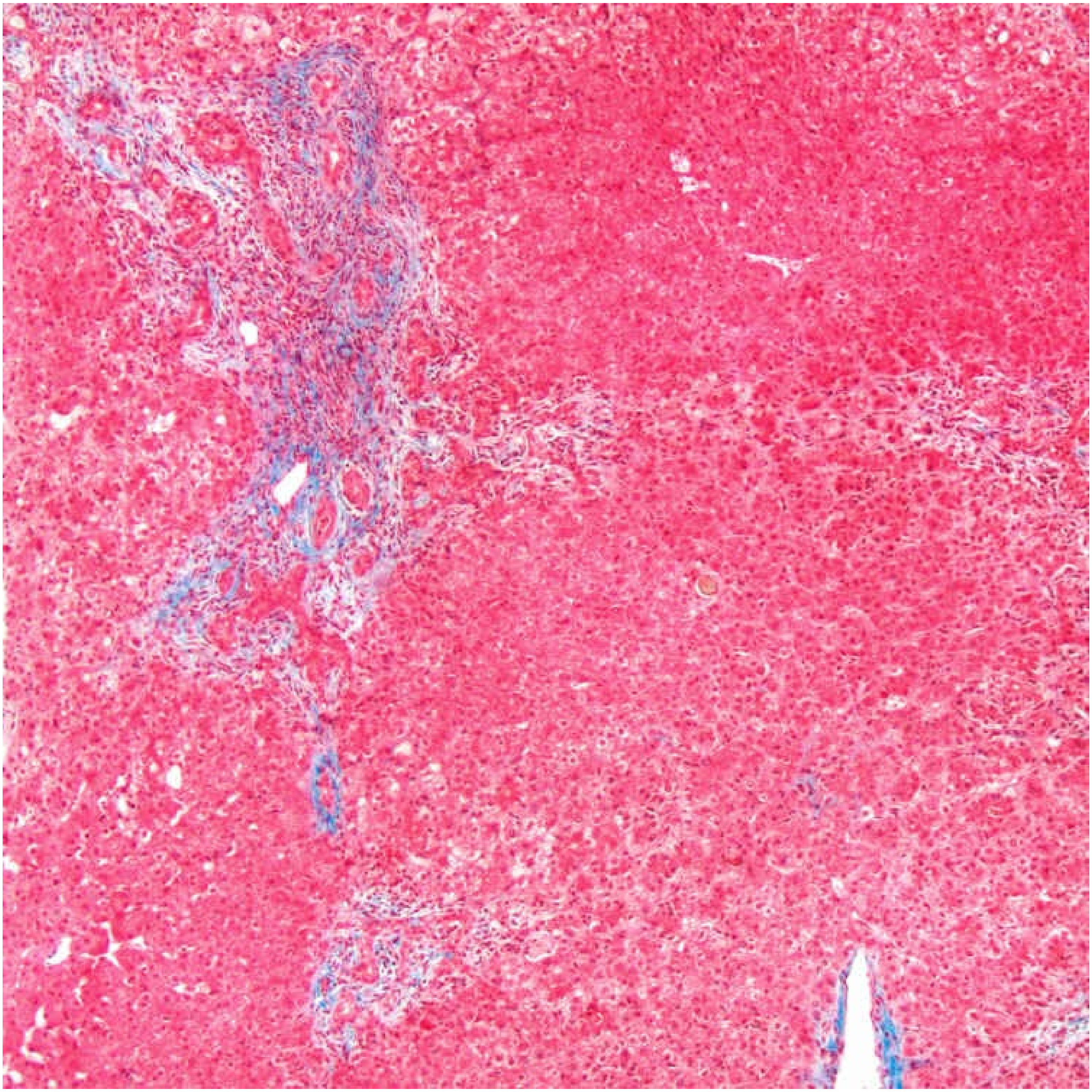
Pathologic Interpretation Pearls

- 1st distinguish neonatal hepatitis-like pattern of injury from obstructive-type pattern of injury
  - If obstructive-type pattern of injury is favored, in addition to biliary atresia, consider other etiologies that can cause this pattern
    - Variable amount of ductular reaction can be seen in many conditions

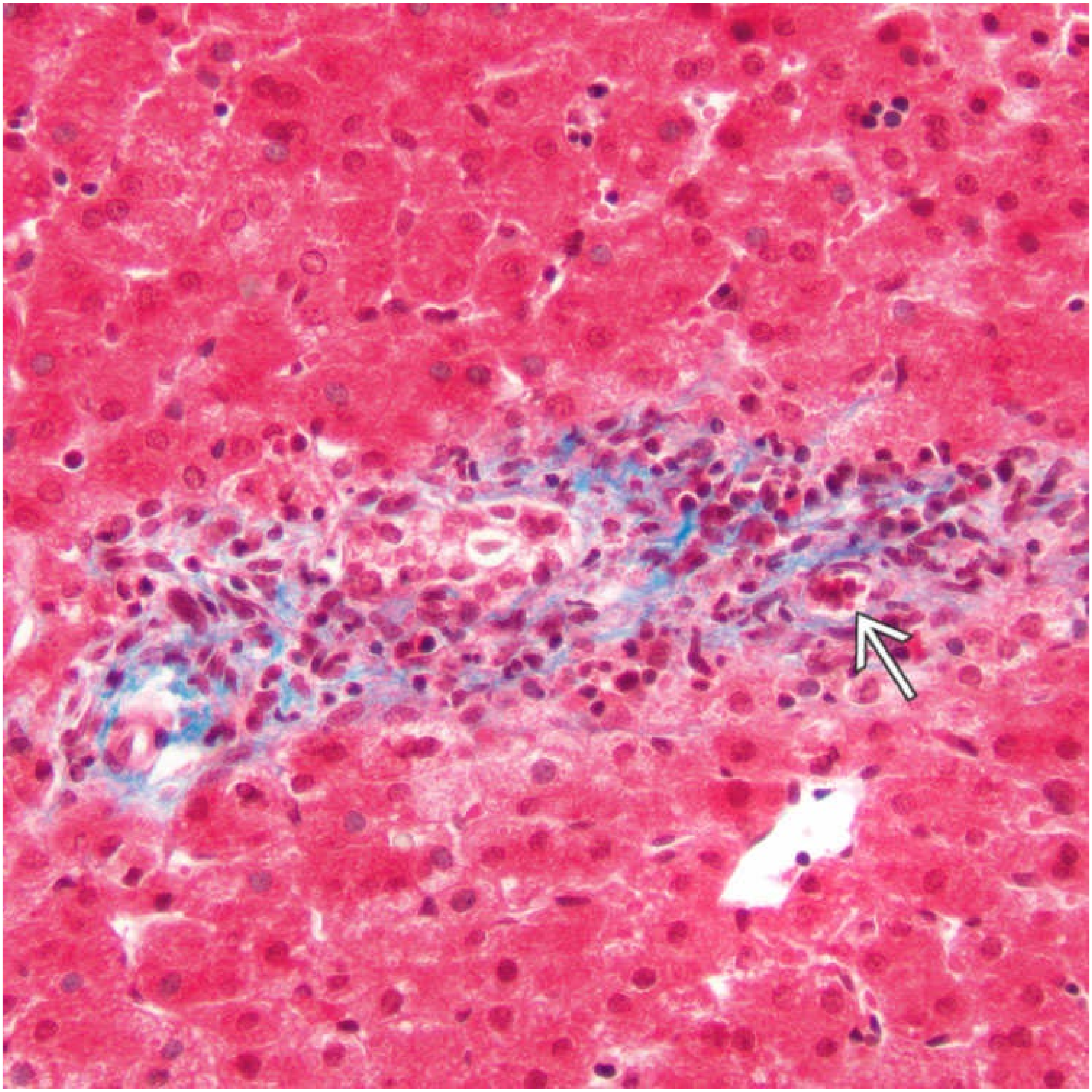


Nonspecific Features of Biliary Atresia

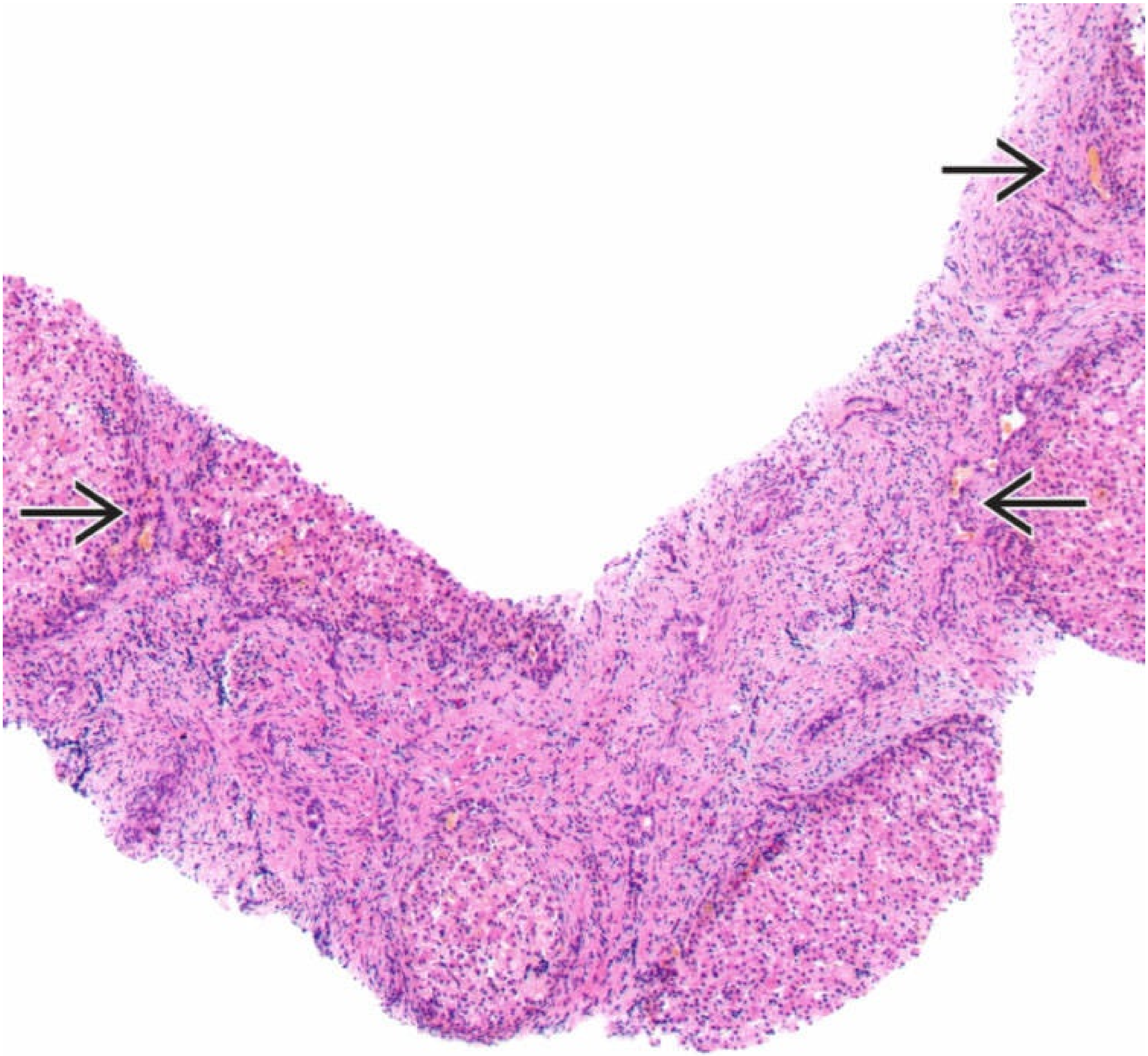
This infant's biopsy at 4 weeks was not diagnostic of BA. Only minimal ductular reaction → is seen in portal tract, along with lobular cholestasis and a few centrizonal multinucleated giant cells.



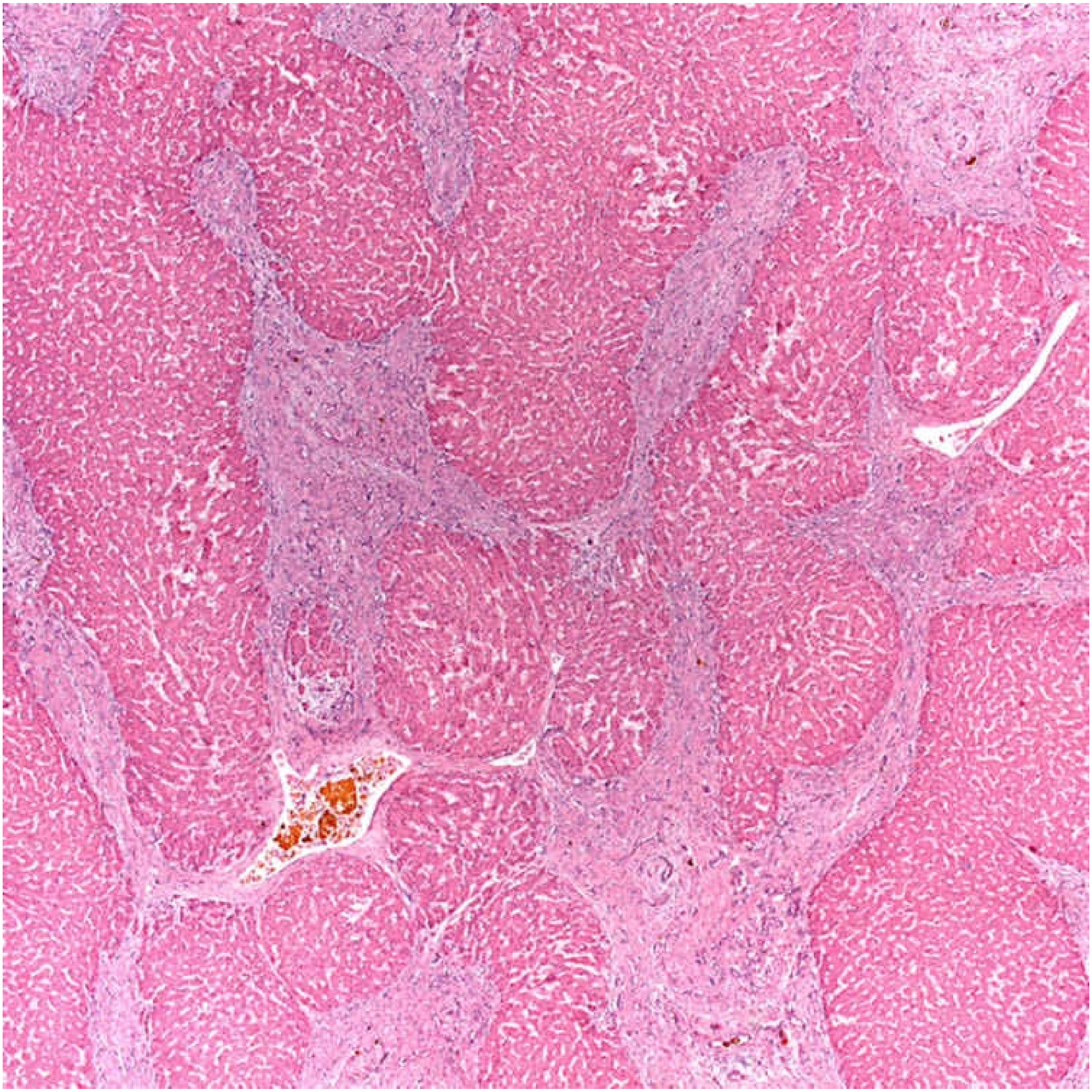
Fibrosis and Ductular Reaction
Portal tract in a 5-week-old neonate with BA already shows marked expansion by fibrosis and early septal formation as well as ductular reaction supportive of an obstructive pattern of injury.



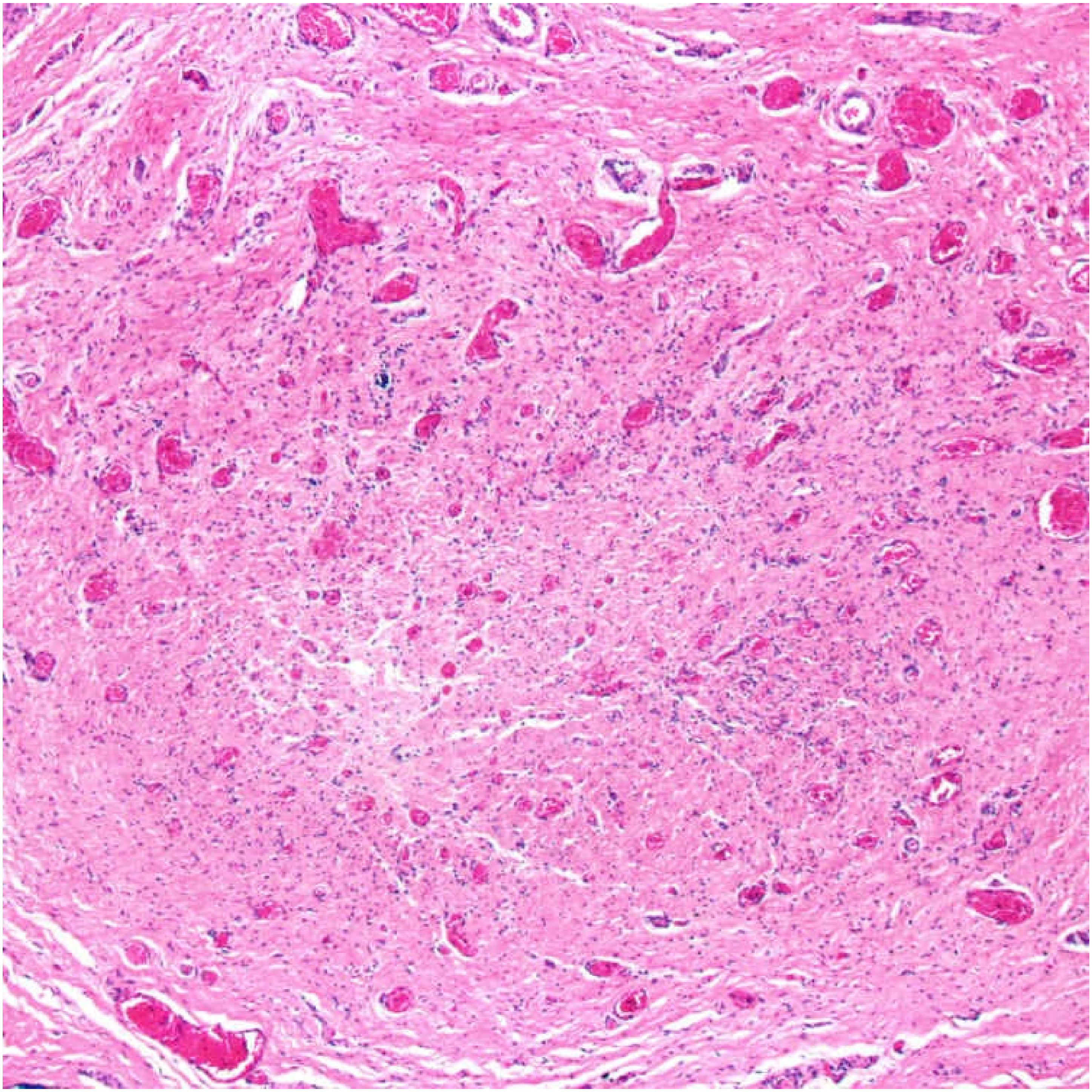
Bile Plug
Most of the portal tracts in this liver biopsy were unremarkable except for this single focus with a bile plug ⇒ on trichrome stain. In the appropriate clinical context, as in this liver biopsy from a 4 week old, this finding suggests an obstructive pattern of injury.



Fibrosis
Liver biopsy from a 9-week-old infant is cirrhotic with wide bands of fibrosis between the nodules of remaining hepatocytes. Note the bile plugs in the ductules →. This infant was clinically diagnosed as BA.

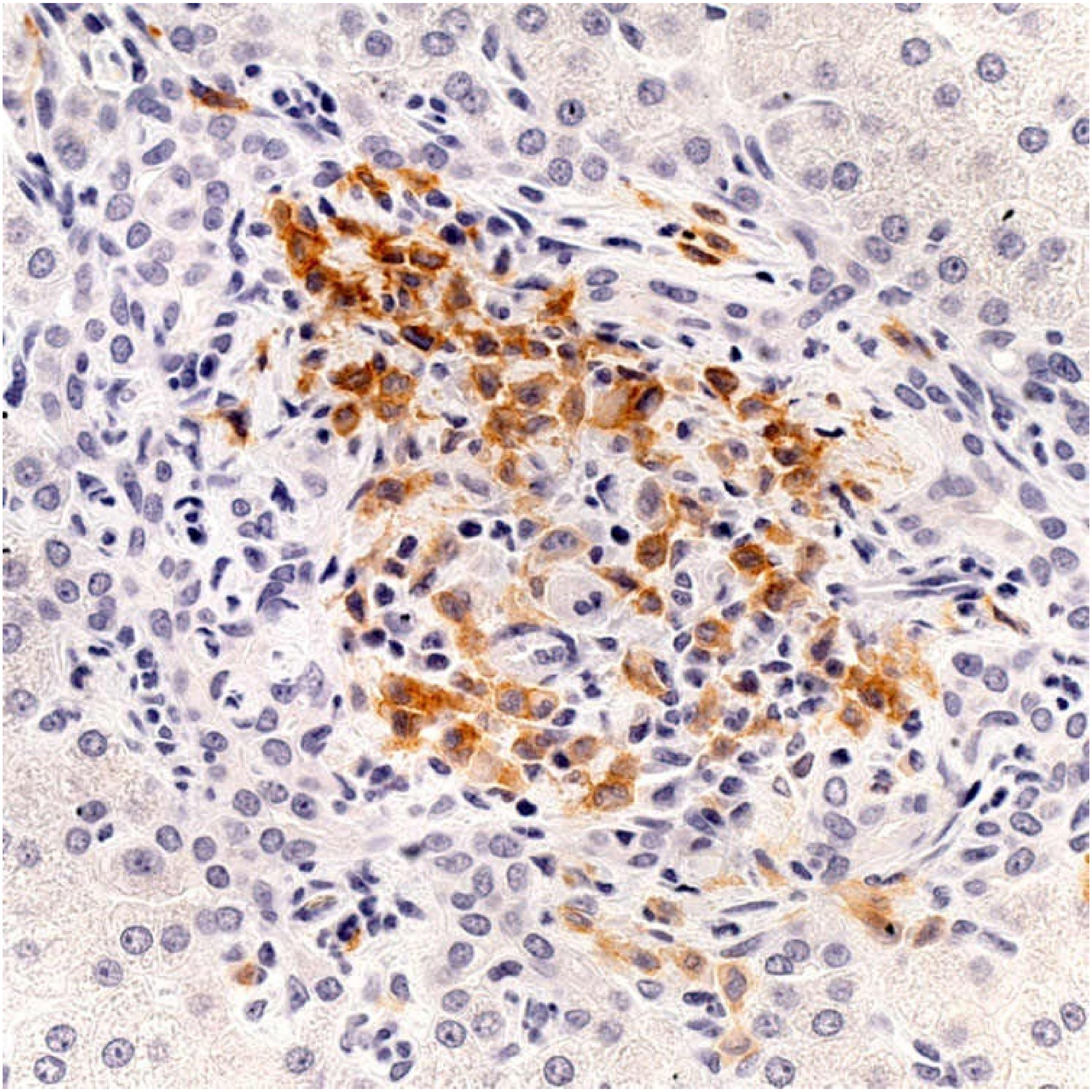


Irregular Nodules of Parenchyma
Liver explanted from a 7 month old with BA shows irregular nodules of parenchyma separated by portal-to-portal bridging fibrosis, resulting in the architectural distortion typical of biliary cirrhosis.

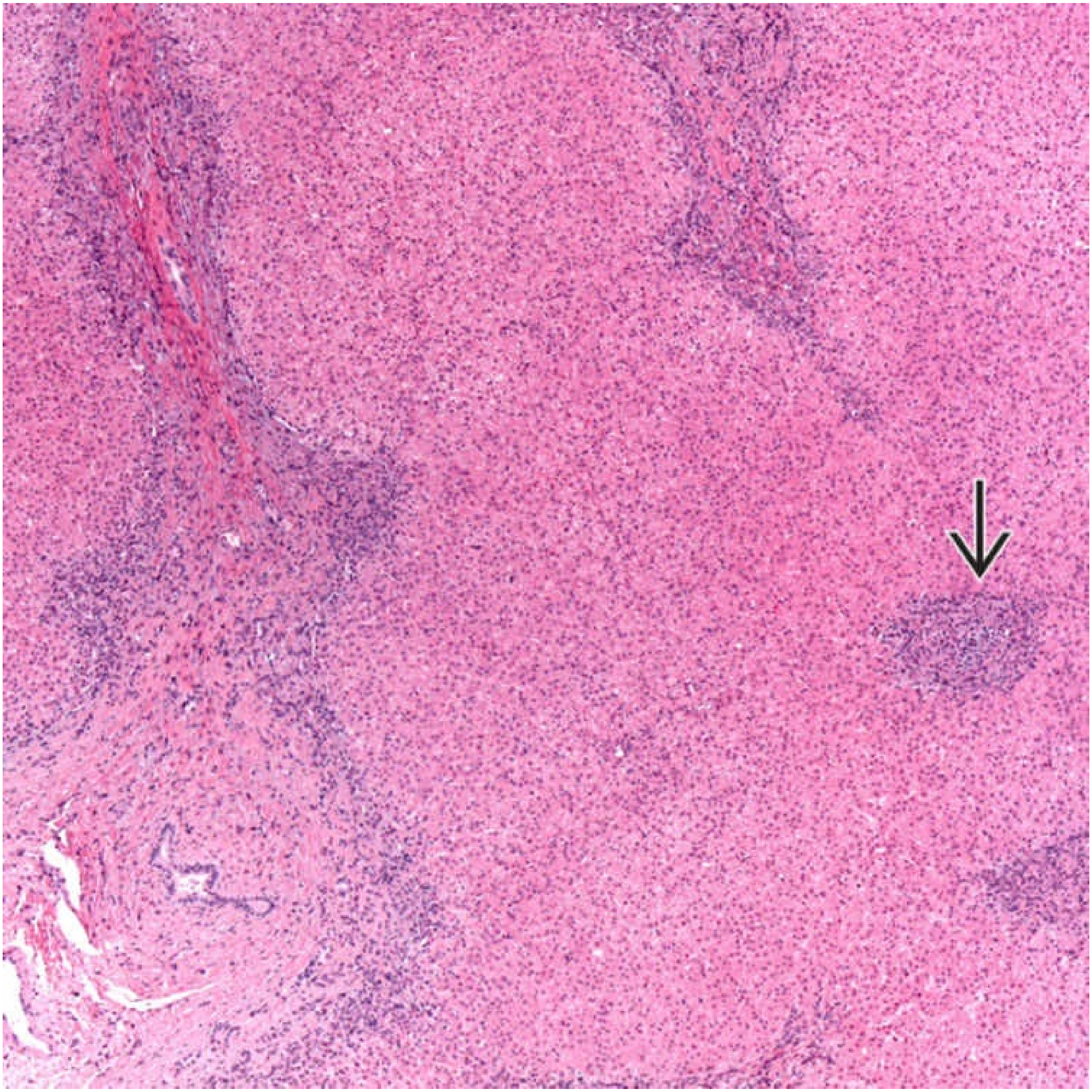


Biliary Remnant

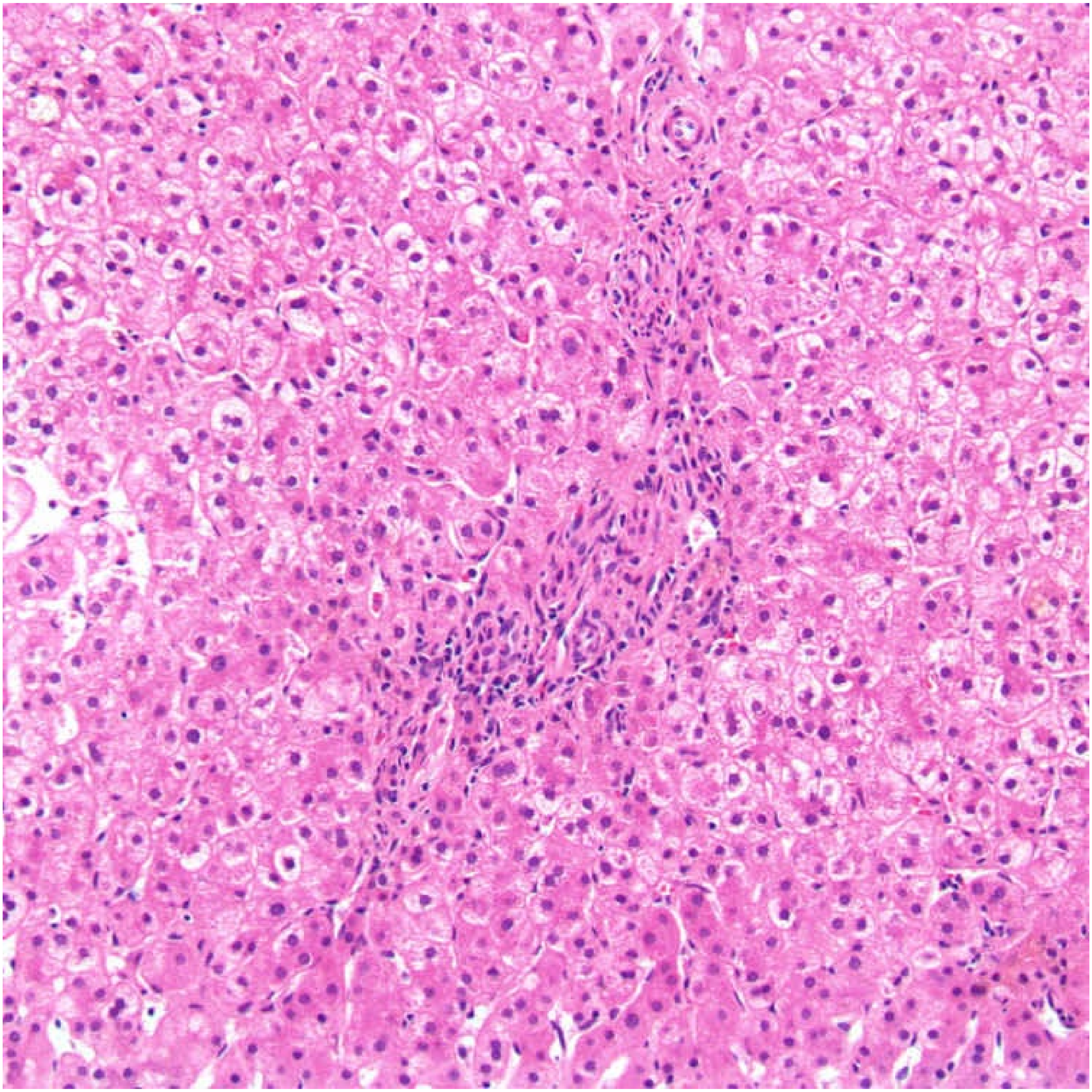
Biliary remnant from a 9 week old shows no bile duct lumen but rather fibrovascular tissue cuffed by a vascular plexus. This section was taken near the hilum of the liver. Distal to this section, a single patent bile duct lumen was found.



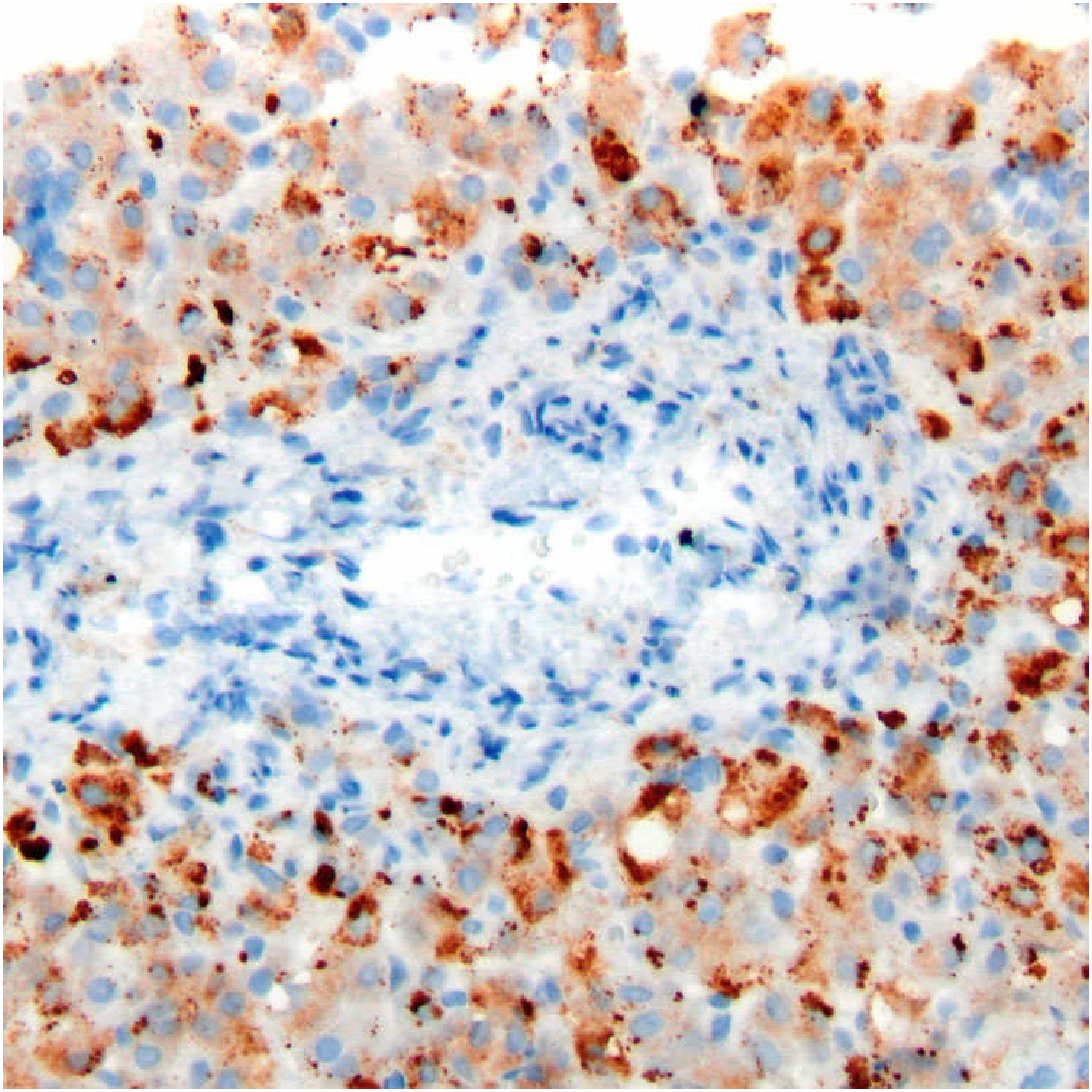
CD1a(+) staining of mononuclear infiltrate in a small portal tract provides support for the diagnosis of Langerhans cell histiocytosis. However, the infiltrate was only focally evident. (From DP: Nonneoplastic Pediatrics.)



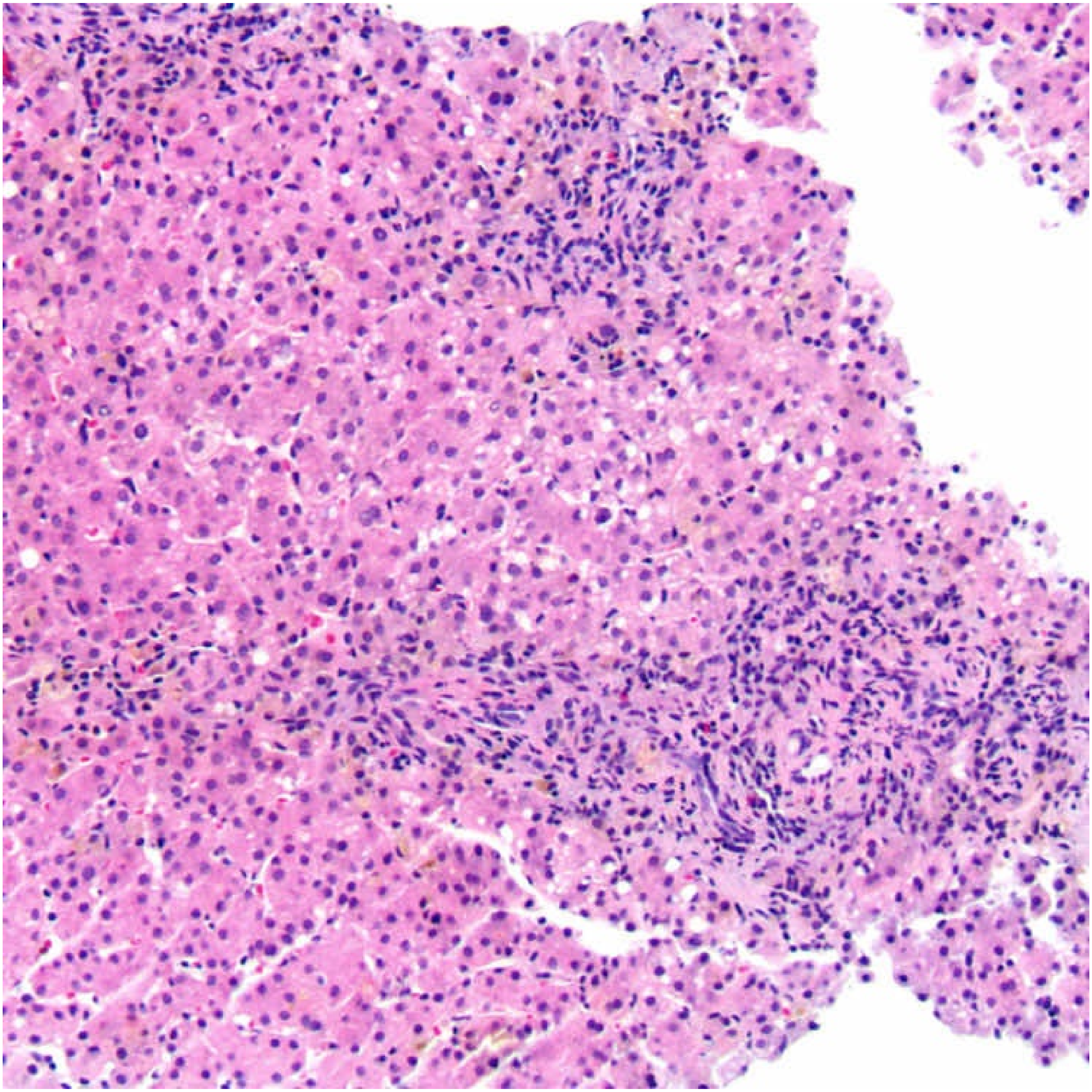
Langerhans cell histiocytosis at low power features expanded portal tracts with significant ductular reaction, mimicking the obstructive pattern of injury seen in BA. However, in a focal small portal tract →, a mononuclear infiltrate is also present.



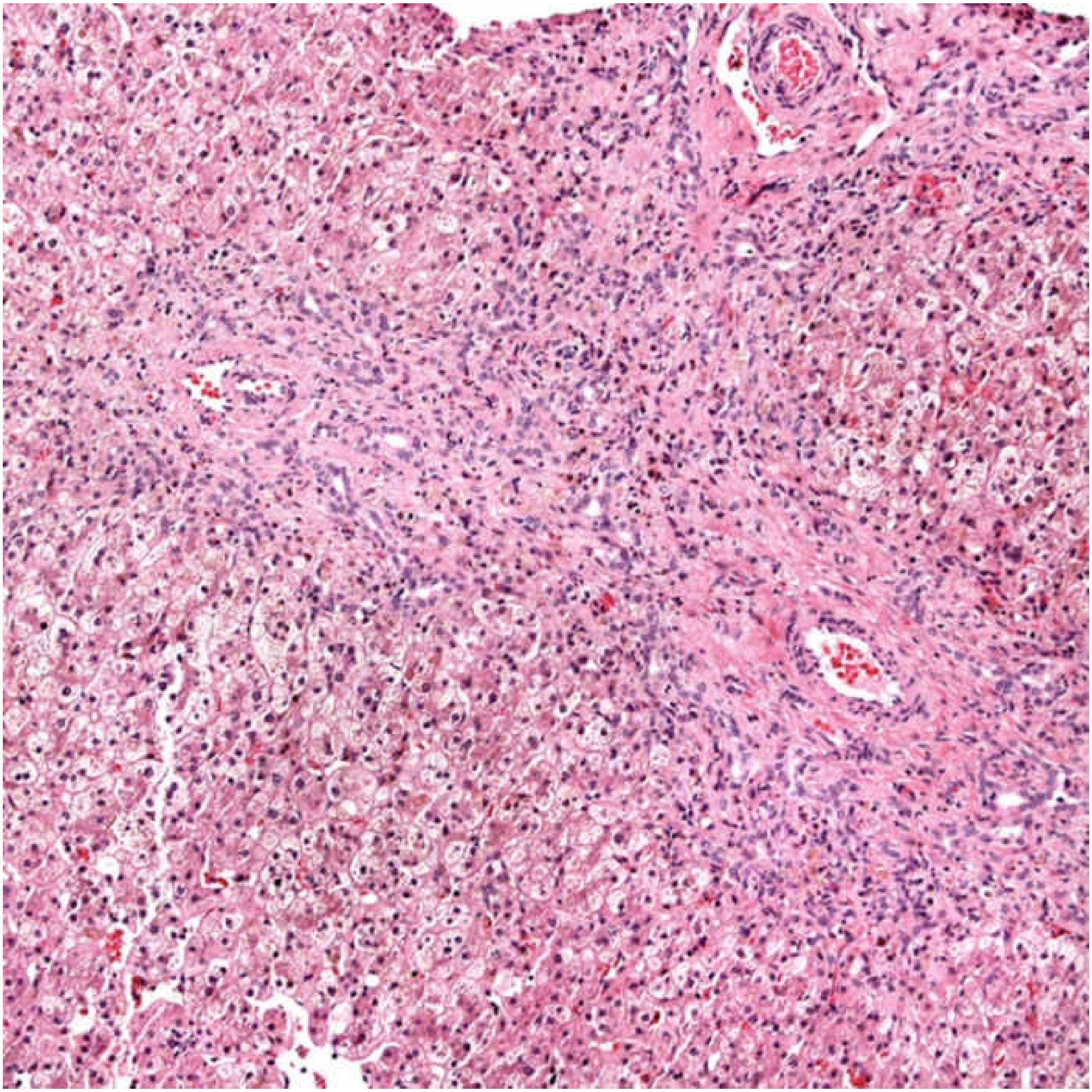
Only focal and minimal ductular reaction is seen in this portal tract from the liver biopsy from an 8 week old who was on total parenteral nutrition (TPN) since birth. A diagnosis of BA is unlikely with this morphology.



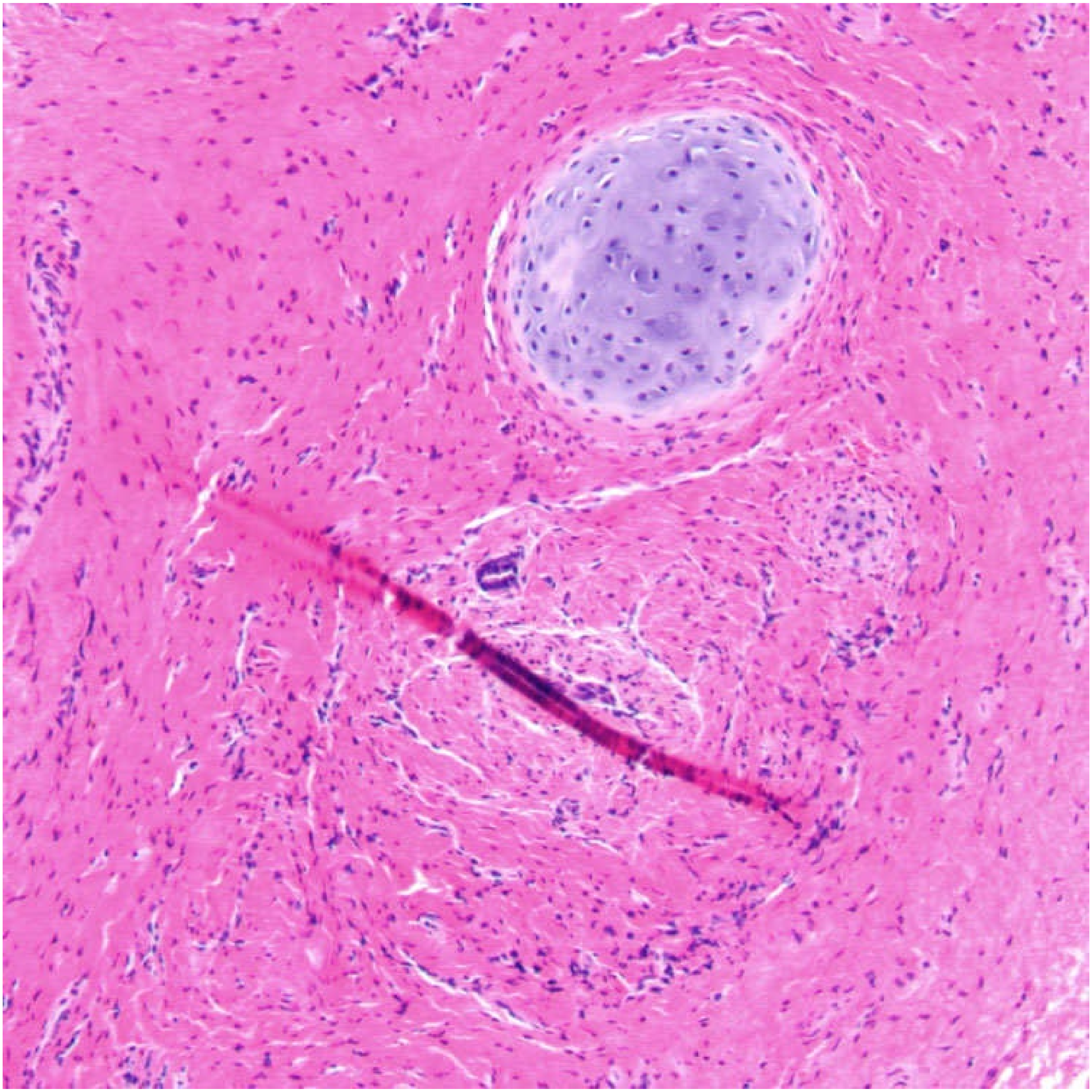
α-1-antitrypsin staining is seen in periportal hepatocytes in this biopsy specimen from a 7 week old with α-1-antitrypsin deficiency. Cytoplasmic globules were not apparent on H&E and are not typically visible until > 12 weeks of age.



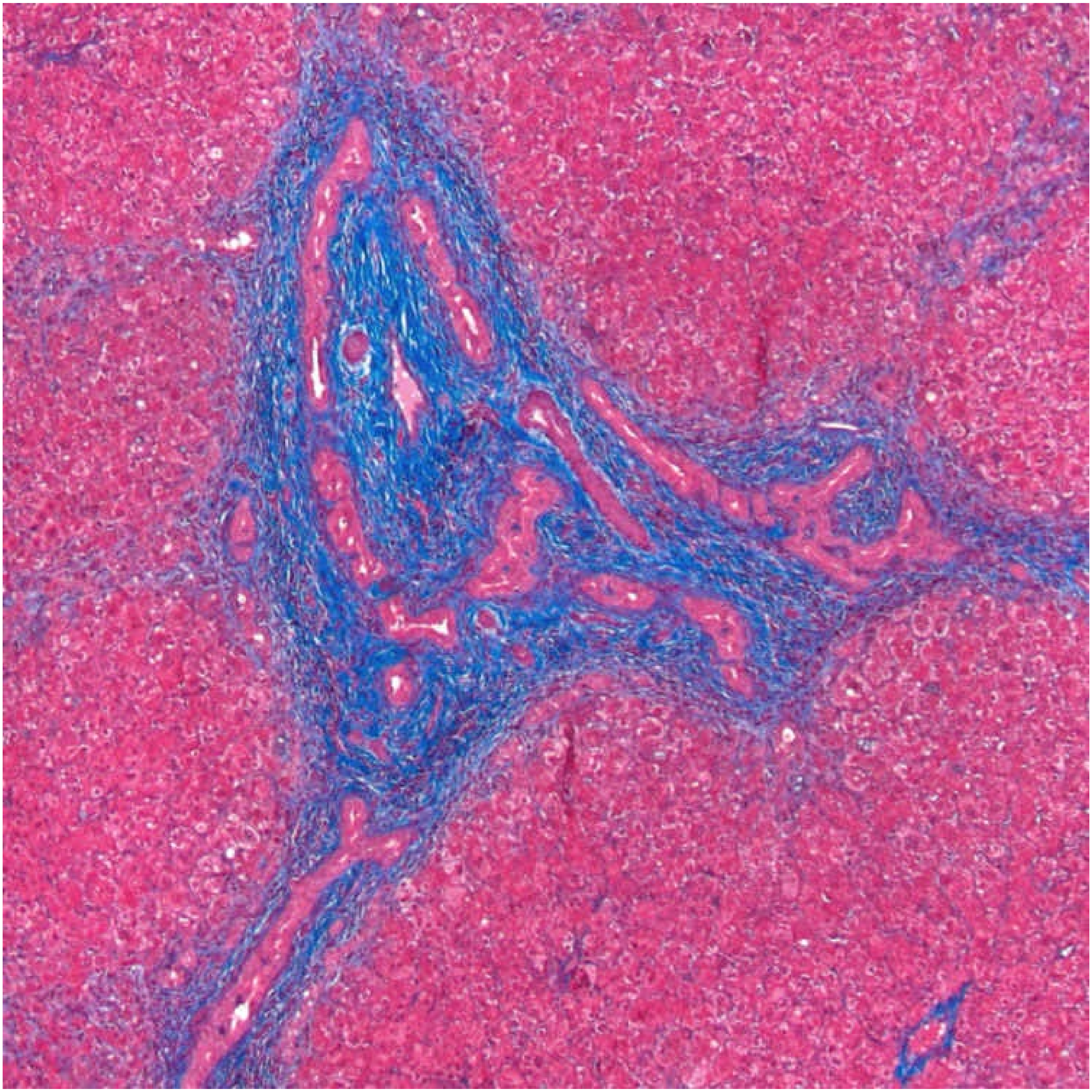
Liver biopsy specimen from a 7-week-old infant with α-1-antitrypsin deficiency has cholestasis and mildly expanded portal tracts with ductular reaction. These changes in the liver can be indistinguishable from BA patients.



In a 9-week-old infant who had been on TPN since birth, liver displays portal tract expansion with extensive ductular reaction. The differential diagnosis includes other disorders with an obstructive pattern of injury.



H&E section in portal hepatis shows focal hyaline cartilage, an unusual finding in biliary atresia.



This discontinuous, semicircumferential configuration of bile ducts with a central fibrovascular core, reminiscent of ductal plate malformation, can be found in BA. Its presence does not distinguish between the clinical forms (prenatal vs. postnatal), however.

SELECTED REFERENCES

1. Schwarz, KB, et al. Extrahepatic anomalies in infants with biliary atresia: results of a large prospective North American multi-center study. *Hepatology*. 2013; 58(5):1724–1731.
2. Moreira, RK, et al. Biliary atresia: a multidisciplinary approach to diagnosis and management. *Arch Pathol Lab Med*. 2012; 136(7):746–760.
3. Hartley, JL, et al. Biliary atresia. *Lancet*. 2009; 374(9702):1704–1713.
4. Sokol, RJ, et al. Screening and outcomes in biliary atresia: summary of a National Institutes of Health workshop. *Hepatology*. 2007; 46(2):566–581.

5. Fouquet, V, et al. Long-term outcome of pediatric liver transplantation for biliary atresia: a 10-year follow-up in a single center. *Liver Transpl*. 2005; 11(2):152–160.
6. Kahn, E. Biliary atresia revisited. *Pediatr Dev Pathol*. 2004; 7(2):109–124.
7. Azar, G, et al. Atypical morphologic presentation of biliary atresia and value of serial liver biopsies. *J Pediatr Gastroenterol Nutr*. 2002; 34(2):212–215.
8. Lefkowitch, JH. Biliary atresia. *Mayo Clin Proc*. 1998; 73(1):90–95.
9. Nietgen, GW, et al. Intrahepatic bile duct loss in biliary atresia despite portoenterostomy: a consequence of ongoing obstruction? *Gastroenterology*. 1992; 102(6):2126–2133.
10. Raweily, EA, et al. Abnormalities of intrahepatic bile ducts in extrahepatic biliary atresia. *Histopathology*. 1990; 17(6):521–527.

Idiopathic Neonatal Hepatitis

KEY FACTS

Terminology

- General term for clinical condition manifested by prolonged jaundice in neonates with variable but definable histologic picture
  - Uniform clinical presentation but broad spectrum of causative disease processes
  - Once known etiologies are excluded, then considered idiopathic
- By mid-2000s, idiopathic neonatal hepatitis (INH) comprised only 15-30% of neonatal cholestasis due to increased ability to detect and diagnose metabolic and genetic disorders previously considered idiopathic

Clinical Issues

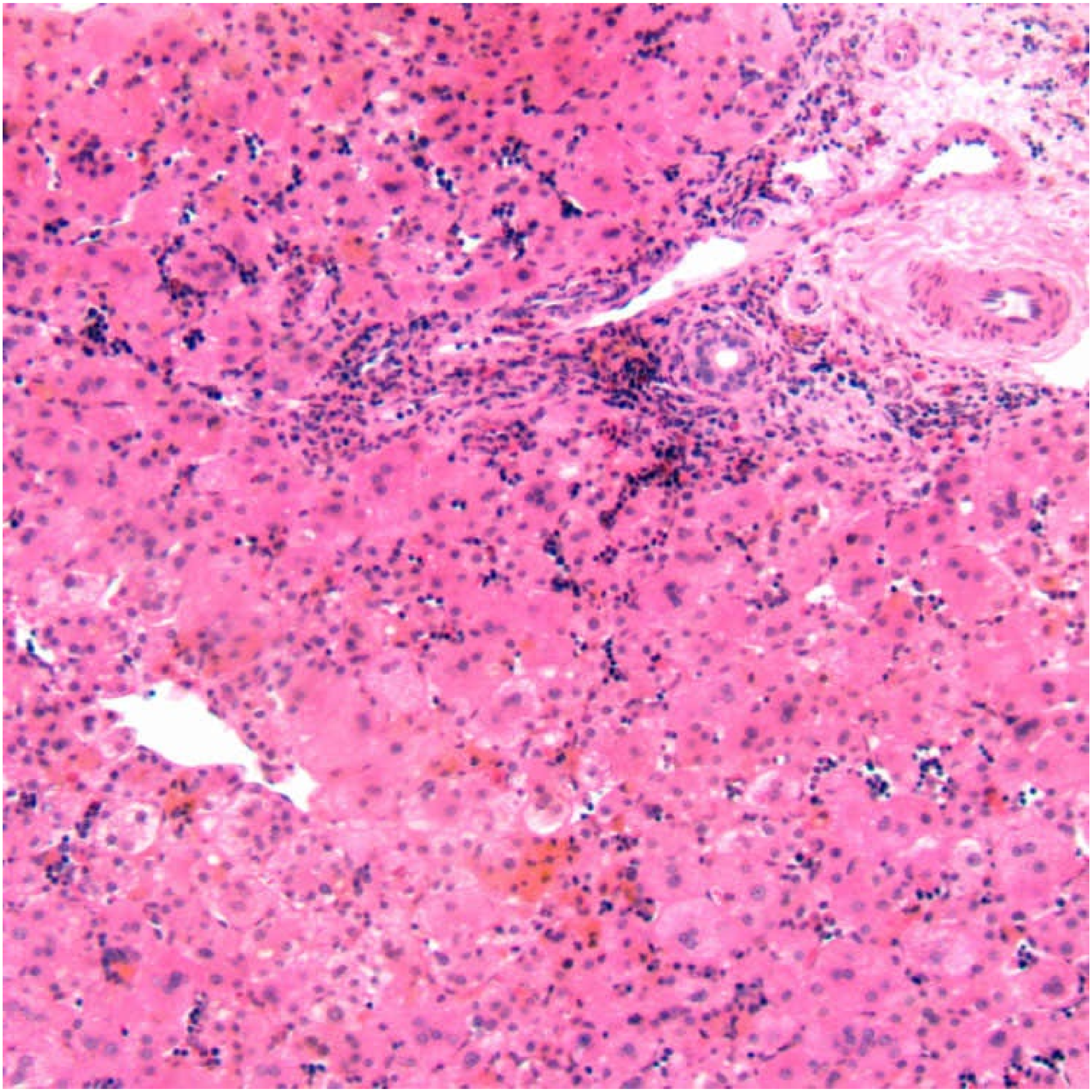
- Jaundice
- Hepatomegaly ± splenomegaly
- Bruising/bleeding due to vitamin K deficiency
- Elevated serum total and conjugated bilirubin
- Variably elevated transaminases

Microscopic

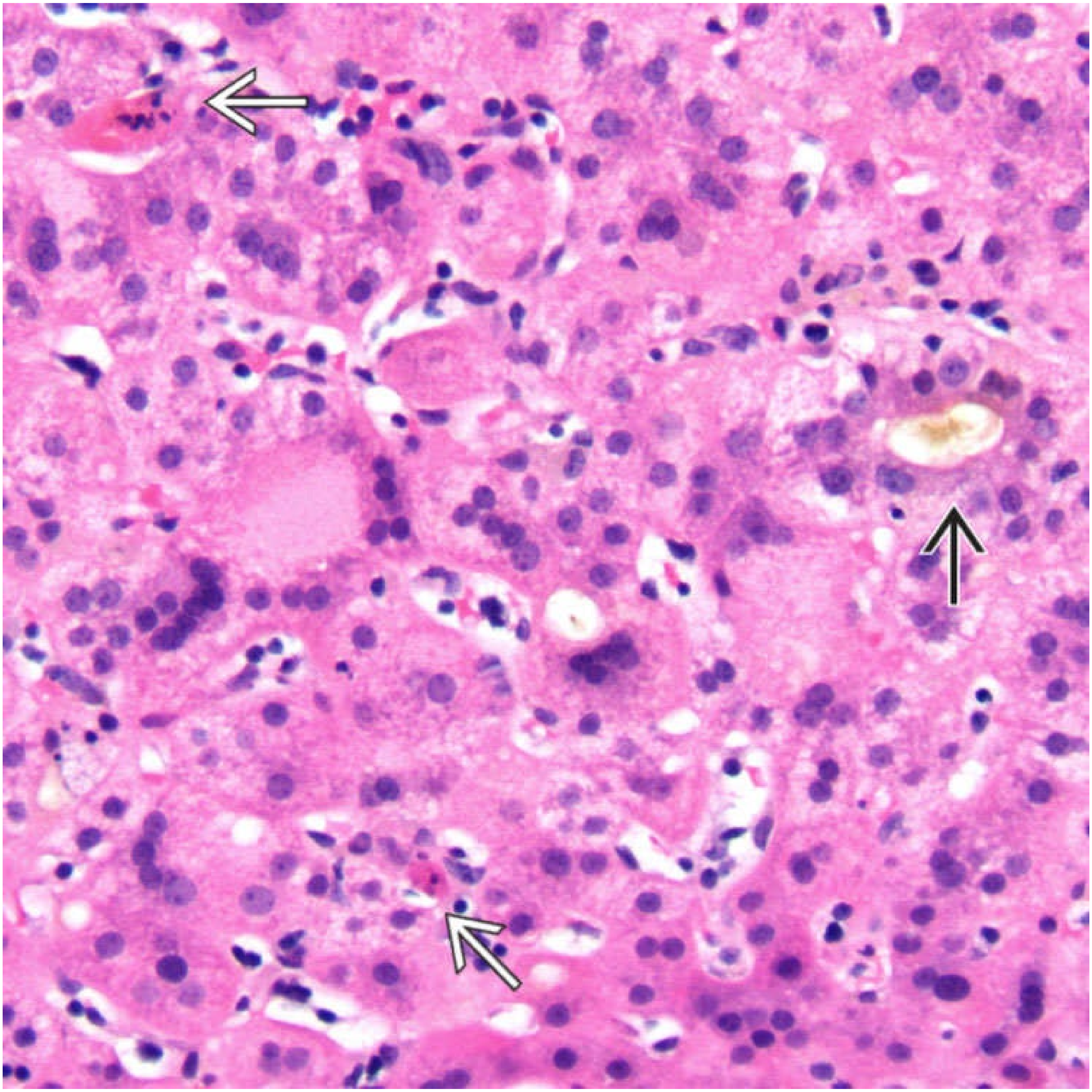
- Lobular disarray with giant cell transformation
- Canalicular and hepatocellular cholestasis
- Minimal portal changes
- Preserved bile ducts
- Prominent extramedullary hematopoiesis

Top Differential Diagnoses

- Exclude biliary atresia right away because it requires early surgical intervention
  - If neonatal hepatitis-like pattern of injury present, use clinical information and molecular tests to exclude known disorders
  - INH is diagnosis of exclusion

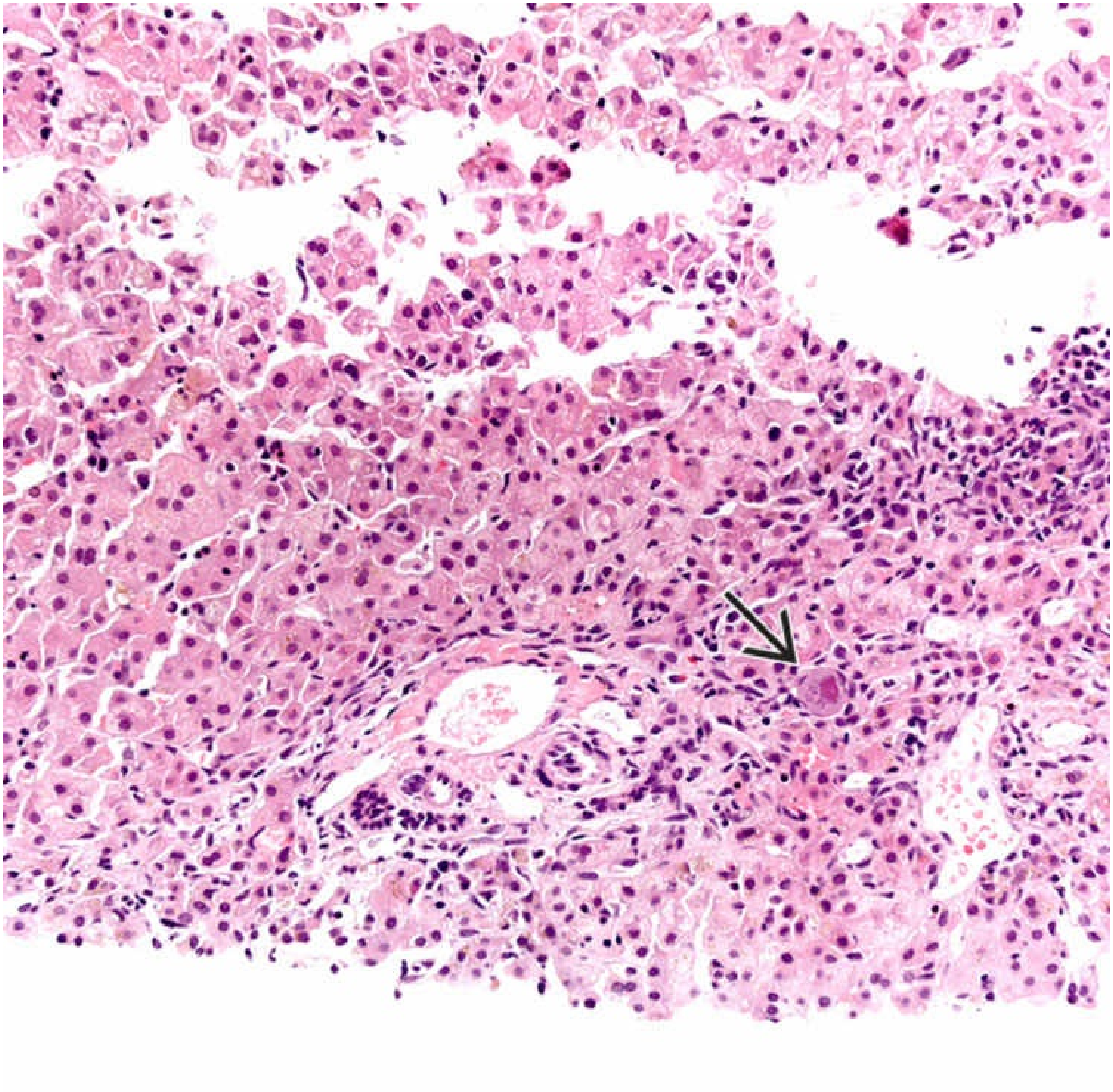


Lobular Giant Cell Change and Extramedullary Hematopoiesis
The characteristic features of idiopathic neonatal hepatitis include lobular giant cell transformation and prominent extramedullary hematopoiesis. Portal changes are minimal, and ductular reaction is absent.

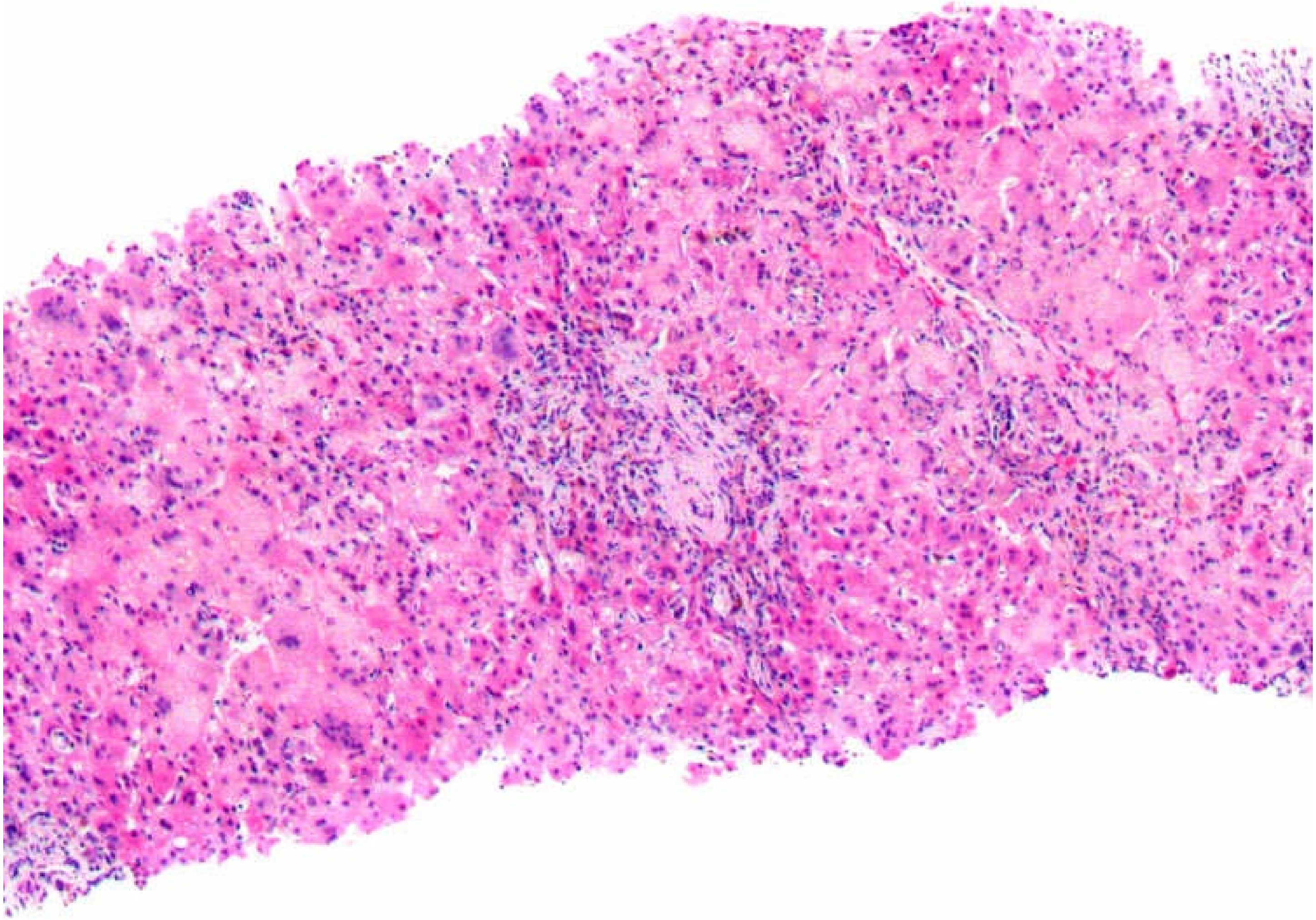


Cholestasis and Giant Cell Transformation

The lobular hepatocytes show giant cell change and scattered apoptotic hepatocytes ⇒, along with canalicular cholestasis and a cholestatic rosette →.



CMV Infection
This case of neonatal hepatitis due to CMV shows a few giant cell hepatocytes along with extramedullary hematopoiesis. A single CMV inclusion → was identified.



Biliary Atresia May Mimic Neonatal Hepatitis
This biopsy from a 9 week old with biliary atresia has features similar to idiopathic neonatal hepatitis, such as giant cell change, but also contains expanded portal tracts with associated ductular reaction.

TERMINOLOGY

Abbreviations

• Idiopathic neonatal hepatitis (INH)

Definitions

• General term for clinical condition manifested by prolonged jaundice in neonates with variable but

definable histologic picture
- Clinicopathologic picture is termed neonatal hepatitis syndrome
  - Uniform clinical presentation but broad spectrum of causative disease processes
    - Once known etiologies are excluded, then considered idiopathic

CLINICAL ISSUES

Epidemiology

- Incidence
  - In early 1970s, 65% of neonatal cholestasis cases were attributed to INH
  - By mid-2000s, INH comprised only 15-30% of neonatal cholestasis
    - Increased knowledge of hepatobiliary physiology, specifically in areas of metabolic and excretory function, and advances in molecular genetics facilitated ability to detect specific underlying etiologies

Presentation

- Prolonged jaundice with pale stools
- Hepatomegaly; splenomegaly in ~ 50%
- Bruising or bleeding due to vitamin K deficiency

Laboratory Tests

- Elevated total and conjugated bilirubin
- Transaminases can be elevated or near-normal

Treatment

- Supportive care
  - Nutritional supplementation and fat soluble vitamin replacement

Prognosis

- Good overall with timely recognition and treatment
  - Little risk of chronic liver disease in most cases of INH

MICROSCOPIC

Histologic Features

- Lobular disarray with giant cell transformation
  - Lobular inflammation may be mild or absent
  - Variably present apoptotic hepatocytes
- Minimal portal inflammation

- Canalicular and hepatocellular cholestasis ± pseudorosettes
- Prominent extramedullary hematopoiesis, both myelopoiesis and erythropoiesis
- Bile ducts are intact and not decreased
- Histology findings are nonspecific and cannot reliably determine etiology

DIFFERENTIAL DIAGNOSIS

Biliary Atresia

- Early in disease course, obstructive-type pattern of injury with ductular reaction may not be evident
- Abnormalities of biliary tree on imaging
- Very important to exclude because it requires early surgical intervention

Hypopituitarism

- Histologically indistinguishable from INH, but may have small hypoplastic bile ducts
- Clinical features include dysmorphic facial features, hypotonia, hypoglycemia, micropenis, optic nerve hypoplasia
- Septo-optic dysplasia: Patients can have hypopituitarism and neonatal hepatitis

Paucity of Intrahepatic Bile Ducts

- Reduction of bile duct numbers
- Other clinical features if part of a syndrome

α-1-Antitrypsin Deficiency

- Low serum α-1-antitrypsin level
- Abnormal protease inhibitor (PiZZ or PiSZ) phenotype
- Cytoplasmic globules not apparent on H&E at < 12 weeks of age

Infections

- TORCH infections (evaluate with serologic tests or culture)
    - Carefully examine liver biopsy for viral inclusion indicative of CMV or herpes simplex
- Other viruses, including herpes zoster, HIV
- Bacterial infections, such as congenital syphilis and *Listeria*

Bile Acid Synthetic Defects

- Giant cell hepatitis is pattern of injury that may be seen
- Normal levels of serum γ-glutamyl transpeptidase
- Low or normal levels of serum bile acids
- Identification of specific metabolic defect by analysis of urine by fast atom bombardment-mass spectrometry & gas chromatography-mass spectrometry

Bile Salt Export Protein Deficiency (Progressive Familial Intrahepatic Cholestasis Type 2)

- Lobular fibrosis along with giant hepatocytes
  - Mutations in *ABCB11* gene encoding bile salt export protein (BSEP)
  - Negative BSEP canalicular staining
- Normal levels of serum γ-glutamyl transpeptidase

Other Rare Conditions

- Neonatal lupus erythematosus, severe combined immunodeficiency, neonatal hemochromatosis, cystic fibrosis, and Seckel syndrome

SELECTED REFERENCES

1. Davit-Spraul, A, et al. ATP8B1 and ABCB11 analysis in 62 children with normal gamma-glutamyl transferase progressive familial intrahepatic cholestasis (PFIC): phenotypic differences between PFIC1 and PFIC2 and natural history. *Hepatology*. 2010; 51(5):1645–1655.
2. Balistreri, WF, et al. Whatever happened to “neonatal hepatitis”? *Clin Liver Dis*. 2006; 10(1):27–53. [v].
3. Bove, KE, et al. Bile acid synthetic defects and liver disease: a comprehensive review. *Pediatr Dev Pathol*. 2004; 7(4):315–334.
4. Roberts, EA. Neonatal hepatitis syndrome. *Semin Neonatol*. 2003; 8(5):357–374.
5. McKiernan, PJ. Neonatal cholestasis. *Semin Neonatol*. 2002; 7(2):153–165.
6. Spray, CH, et al. Investigation and outcome of neonatal hepatitis in infants with hypopituitarism. *Acta Paediatr*. 2000; 89(8):951–954.

Paucity of Intrahepatic Bile Ducts (Syndromic)

KEY FACTS

Terminology

- Alagille syndrome: Intrahepatic bile duct hypoplasia progressing to ductopenia that results in chronic cholestasis, associated with other congenital abnormalities
  - Cardiac abnormalities, particularly pulmonary stenosis
  - Skeletal abnormalities, particularly butterfly vertebrae
  - Ocular abnormalities, particularly posterior embryotoxon
  - Characteristic facies

Etiology/Pathogenesis

- Mutations in *J AG1* gene, which encodes ligand for Notch receptor
- Interaction between *JAG1* and *NOTCH2* may be necessary for bile duct maturation

Clinical Issues

- Presents as jaundice before age of 6 months

Imaging

- Hepatobiliary scan
  - Excretion of technetium-labeled iminodiacetic dye typically absent, mimicking extrahepatic biliary atresia
- Cholangiography
  - May show bile duct hypoplasia

Microscopic

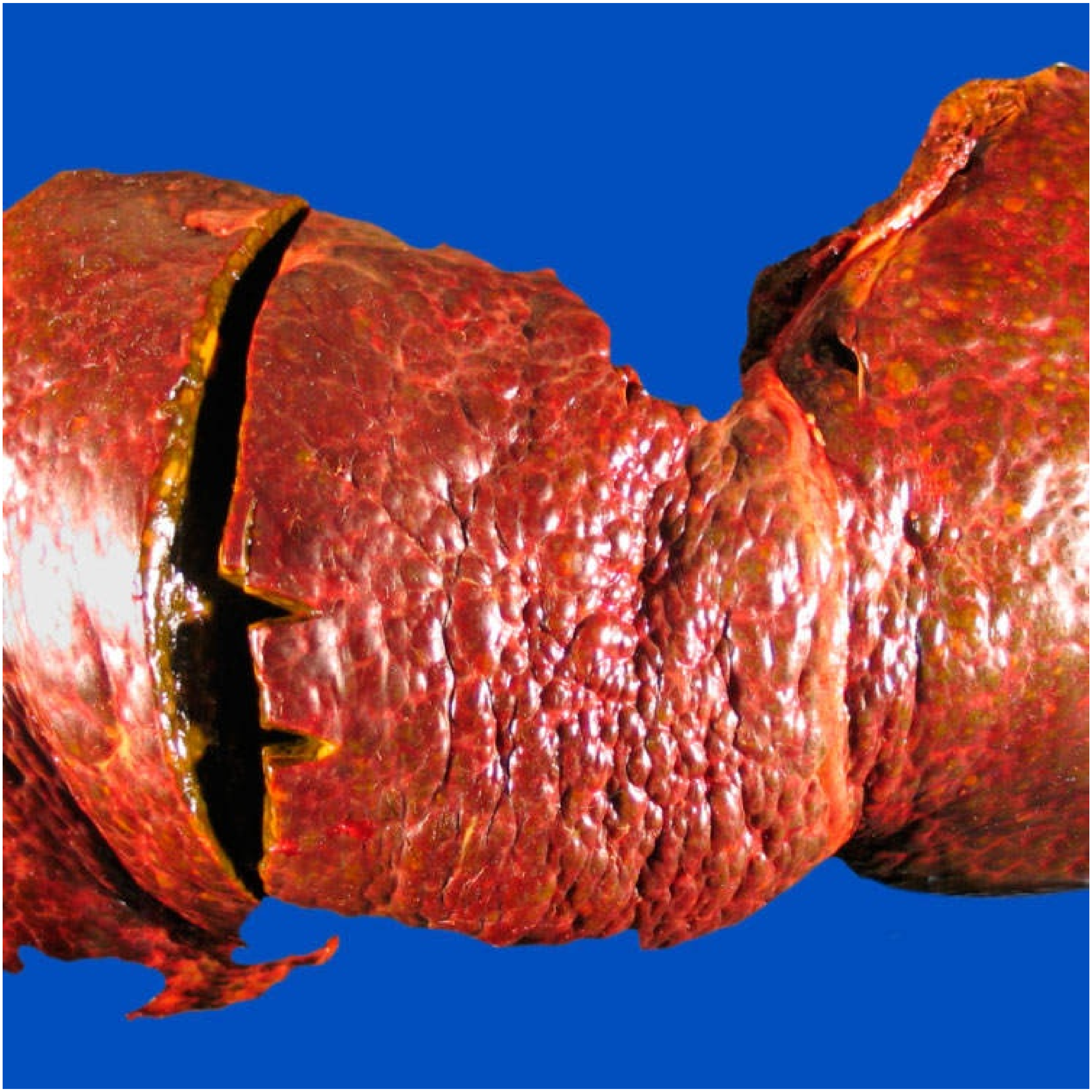
- Early in life, bile duct destruction, bile ductular reaction, and inspissated bile in ductules can be confused with biliary atresia
- As patient ages, liver shows evolving ductopenia

Top Differential Diagnoses

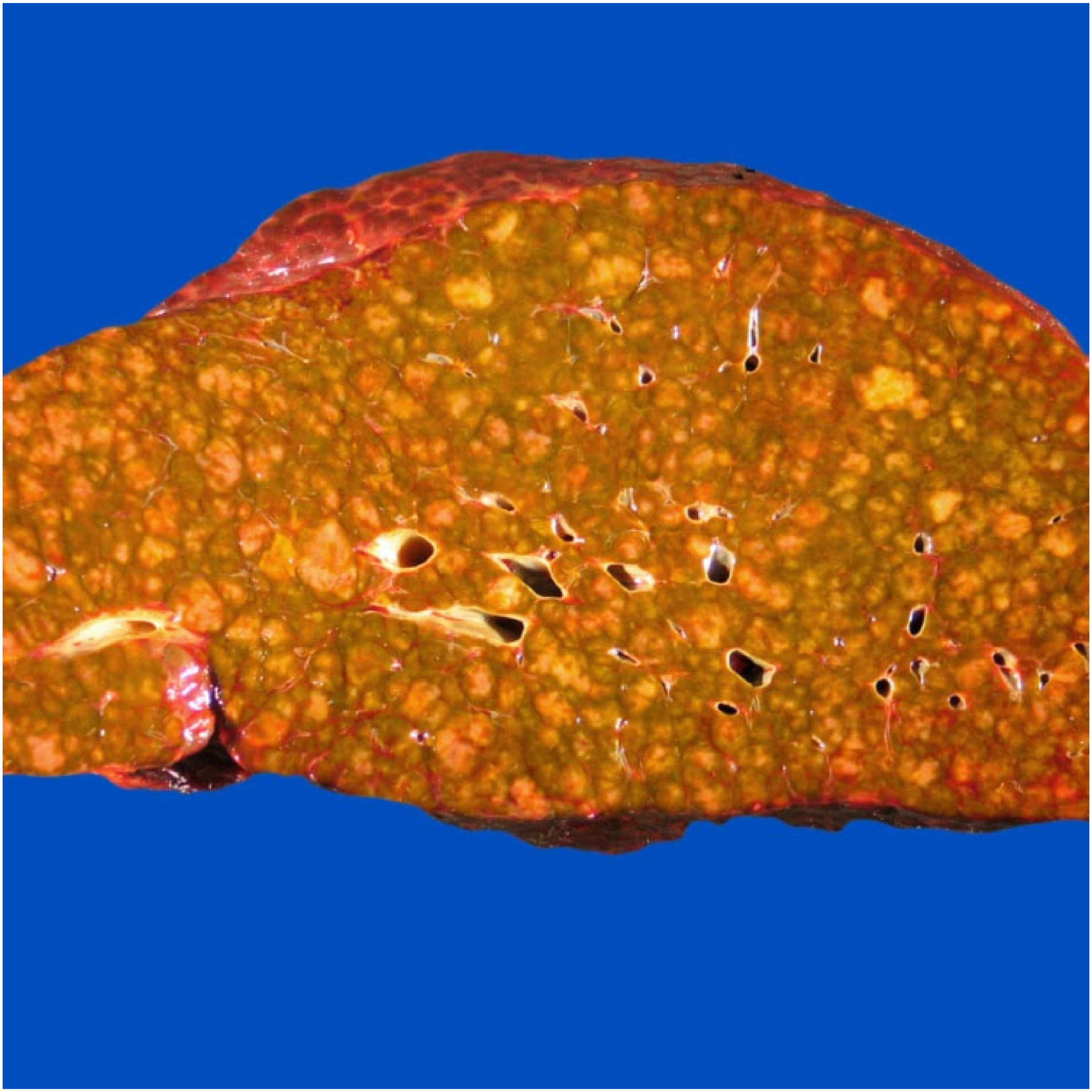
- Extrahepatic biliary atresia
- Paucity of intrahepatic bile ducts (nonsyndromic)

Diagnostic Checklist

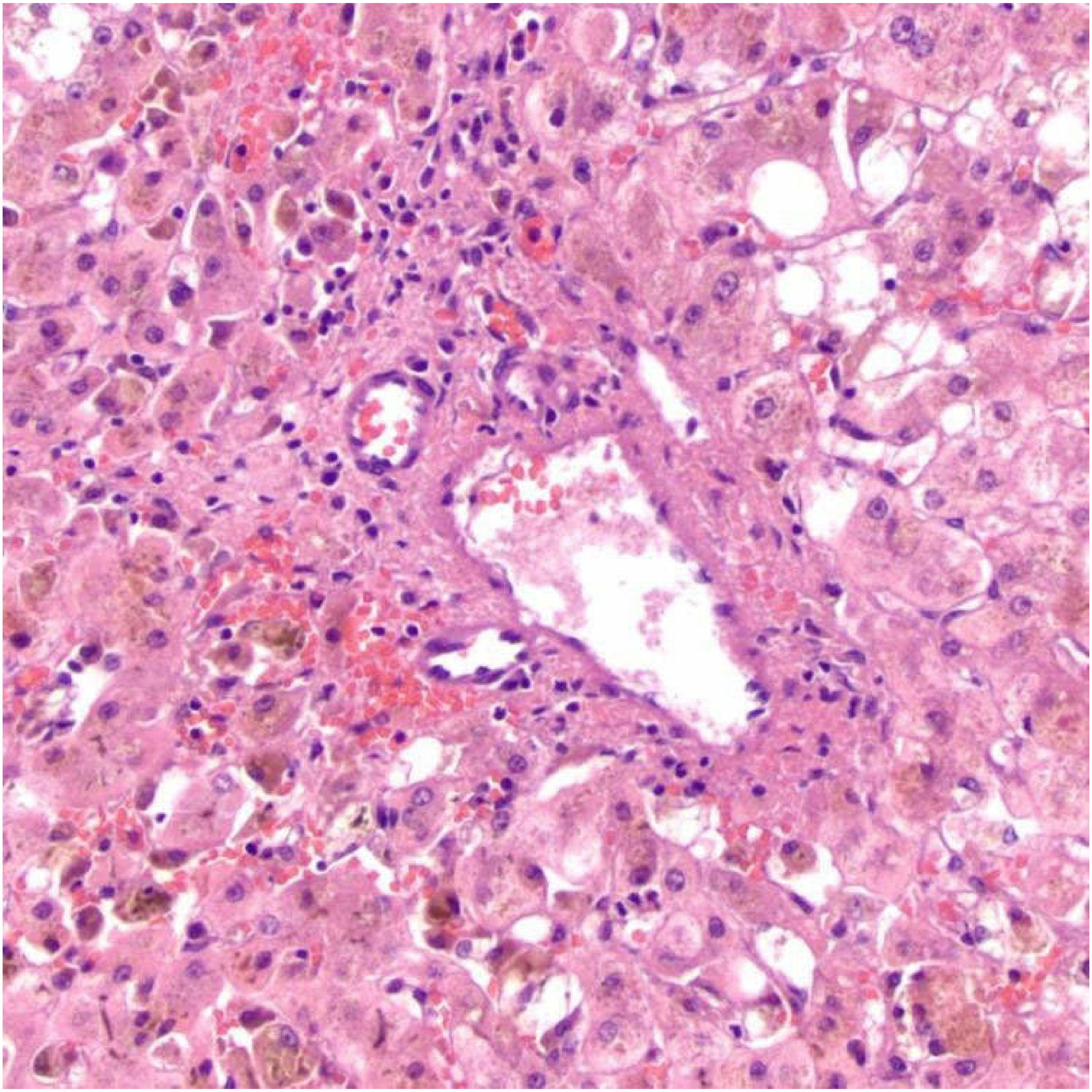
- Liver biopsies in infants with neonatal cholestasis due to Alagille syndrome may be indistinguishable from biliary atresia



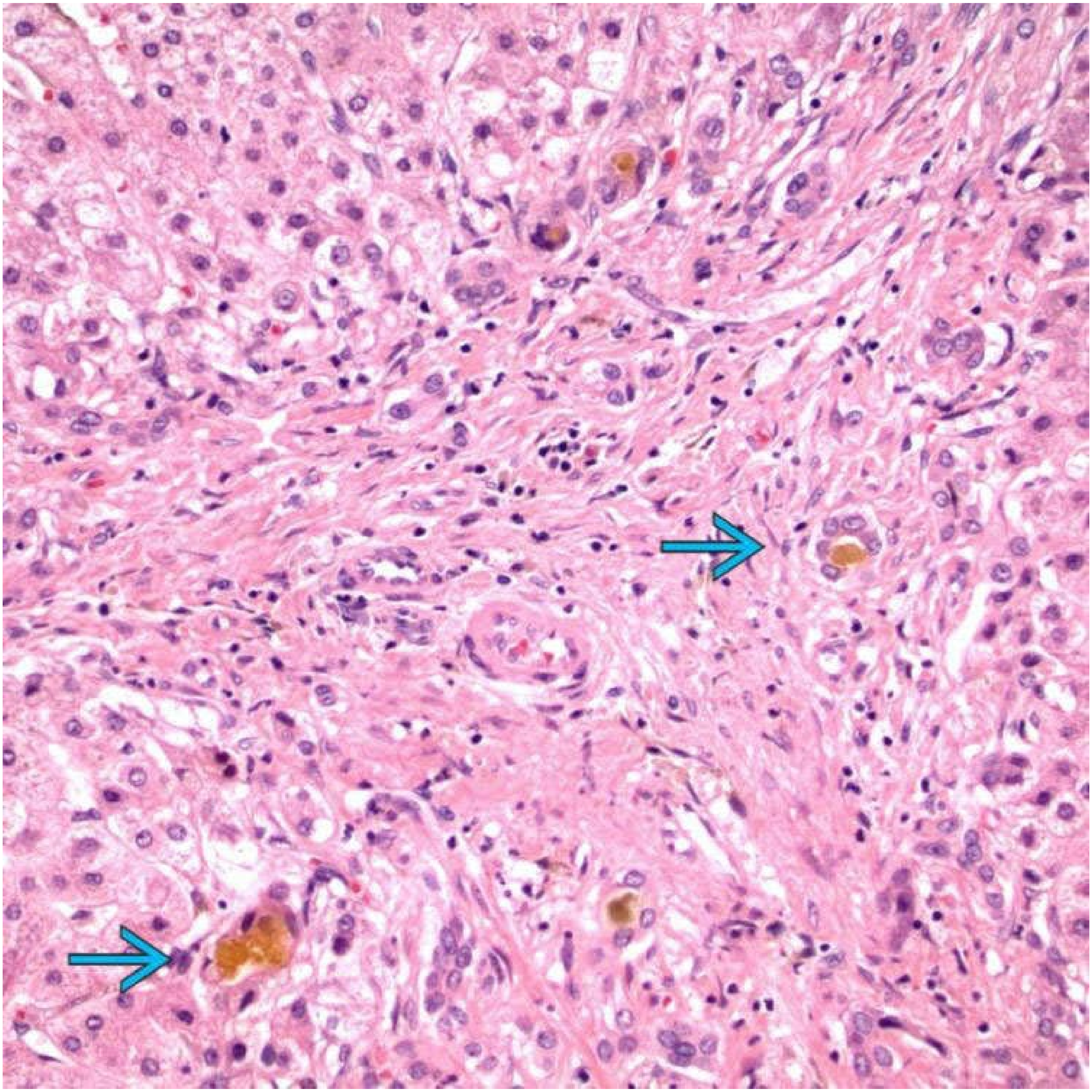
Gross Appearance
Explanted cirrhotic liver from an adult with Alagille syndrome shows a nodular, distorted external surface.



Gross Appearance
Cut surface of cirrhotic liver from an adult with Alagille syndrome shows micronodular cirrhosis, extensive fibrosis, and green discoloration.



Absence of Bile Duct
Portal tract from a patient with Alagille syndrome shows arterioles and veins but no interlobular bile duct.



Bile Ductular Reaction
The edge of a fibrous septum in cirrhotic liver in Alagille syndrome shows bile ductular reaction with inspissated bile in bile ductules →.

TERMINOLOGY

Synonyms

- Alagille syndrome
- Arteriohepatic dysplasia

Definitions

- Syndrome characterized by intrahepatic bile duct hypoplasia and loss, along with at least 3 of the following major clinical features or 2 features in patients with family history
  - Chronic cholestasis
  - Cardiac abnormalities
    - Peripheral pulmonary stenosis, pulmonary valve stenosis, tetralogy of Fallot, aortic stenosis, ventricular septal defects
  - Skeletal abnormalities
    - Butterfly vertebrae, curved phalanges, short ulna
  - Ocular abnormalities
    - Posterior embryotoxon, optic nerve drusen
  - Characteristic facies
    - Broad forehead, deep-set eyes, straight nose, pointed chin

ETIOLOGY/PATHOGENESIS

Genetic Disorder

- Mutations in *JAG1* gene that encodes ligand for Notch receptor seen in up to 90% of patients
  - Interaction between *JAG1* and *NOTCH2* may be important in bile duct formation and maturation to more differentiated state
    - Mutations lead to impaired ductal plate remodeling and subsequent impaired postnatal intrahepatic bile duct development
  - Alternatively, interaction between *JAG1* and *NOTCH4* may be involved in vascular remodeling, and abnormal portal blood vessel remodeling could lead to ductopenia
  - Autosomal dominant inheritance with variable expressivity
- Patients without *JAG1* mutations may have mutations of *NOTCH2* gene (1-2%)

CLINICAL ISSUES

Epidemiology

- Incidence
  - 1 in 100,000
- Age
  - Typically presents in childhood
- Sex
  - No sex predilection
- Ethnicity
  - No ethnic predilection

Presentation

- Jaundice before age of 6 months
    - Consequences of cholestasis
    - – Including xanthomas, fat-soluble vitamin deficiency, pruritus
- Hepatomegaly, splenomegaly, symptoms related to cardiac defects

Laboratory Tests

- Conjugated hyperbilirubinemia
- Increased GGT, alkaline phosphatase, and serum bile acids
- Increased cholesterol

Natural History

- Progresses to cirrhosis in ~ 20% of patients
- Associated with risk of hepatocellular carcinoma

Treatment

- Surgical approaches
    - Partial external biliary diversion and liver transplantation
- Drugs
    - Ursodeoxycholic acid, rifampin, phenobarbitone, cholestyramine to manage cholestasis and pruritus

Prognosis

- In era before liver transplantation, survival to age 20 was 75%
    - ~ 25% of all patients require liver transplantation
    - Presentation with neonatal cholestasis carries worse prognosis
    - 50% require liver transplantation before age of 10 years
- Patients who do not present with neonatal cholestasis may develop liver-related complications later in life
- Presence of cardiac disease predicts increased mortality

Additional Manifestations

- Vascular anomalies
    - Intracranial bleeds account for 25% of deaths
- Renal abnormalities

IMAGING

Hepatobiliary Scan

- Excretion of technetium-labeled iminodiacetic dye typically absent, mimicking extrahepatic biliary

atresia

Cholangiography

- May show bile duct hypoplasia

MICROSCOPIC

Histologic Features

- Early in life (< 3 months), bile duct destruction may be associated with bile ductular reaction
    - Causing confusion with biliary atresia
- As patient ages, liver shows evolving ductopenia, which may be focal
- Later in life, fibrosis and biliary cirrhosis may develop

DIFFERENTIAL DIAGNOSIS

Extrahepatic Biliary Atresia

- Similar presentation to Alagille with conjugated hyperbilirubinemia, small gallbladder, and hypoplasia of common bile duct
- Bile ductular reaction with bile plugs and portal fibrosis on liver biopsy
- Careful examination of hepatobiliary scan and laparotomy may be necessary to distinguish these conditions
- Stigmata of syndromic disorder favors Alagille

Paucity of Intrahepatic Bile Ducts (Nonsyndromic)

- Liver biopsy does not distinguish between syndromic and nonsyndromic paucity of intrahepatic bile ducts
- Stigmata of syndromic disorder favors Alagille

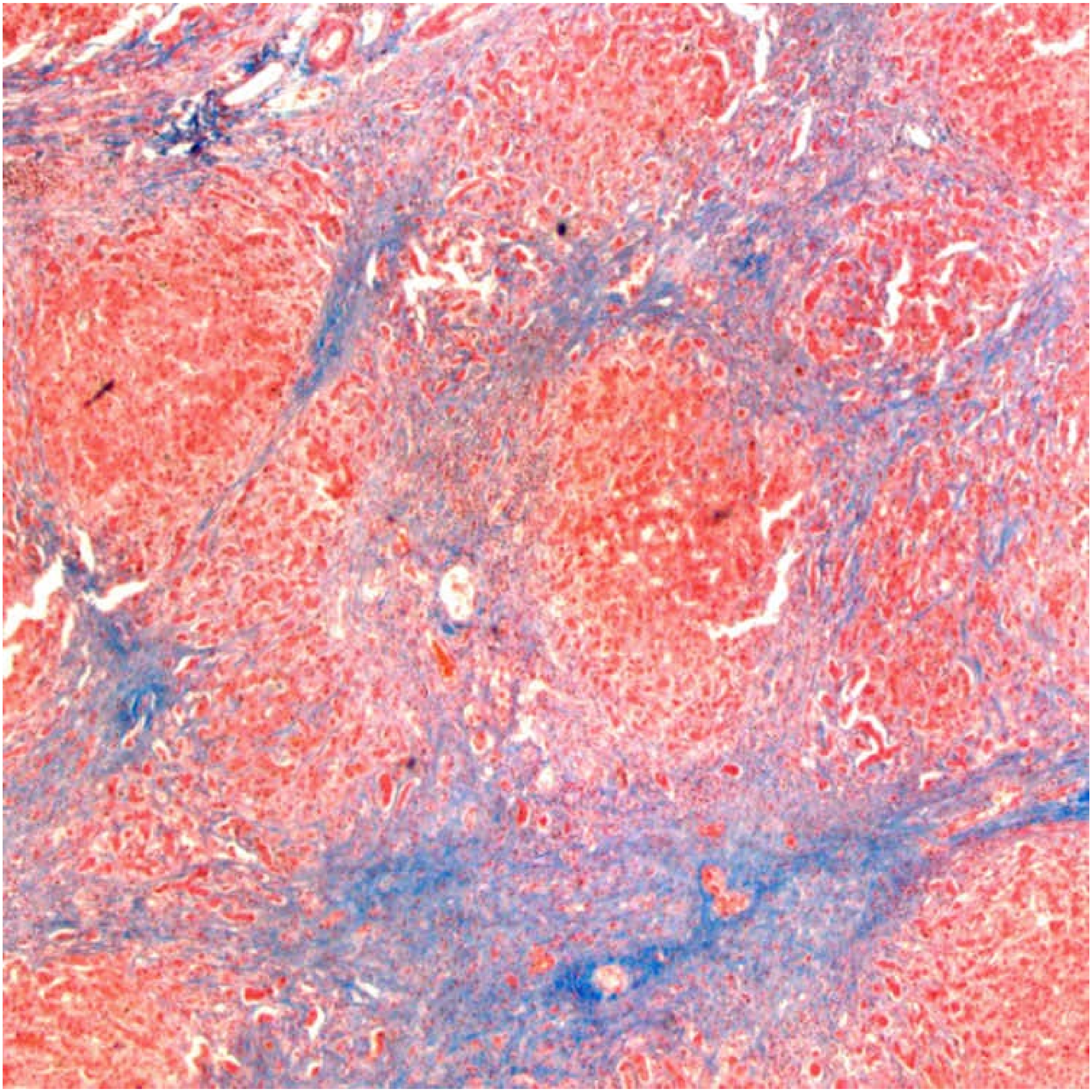
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

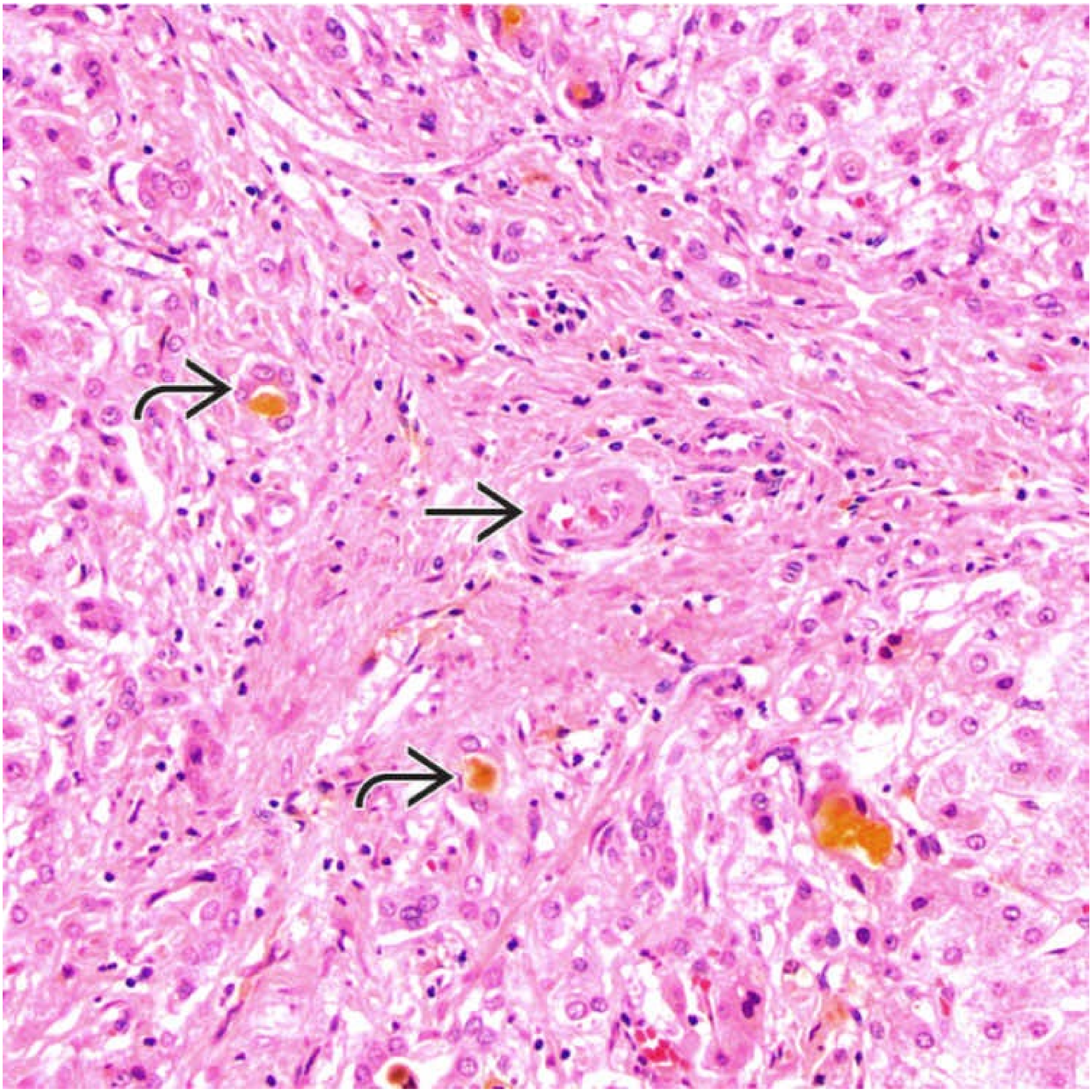
- Bile duct paucity in infant is indication for slit lamp examination and dorsal spine radiograph examination

Pathologic Interpretation Pearls

- Liver biopsies in infants with neonatal cholestasis due to Alagille syndrome may be indistinguishable from biliary atresia

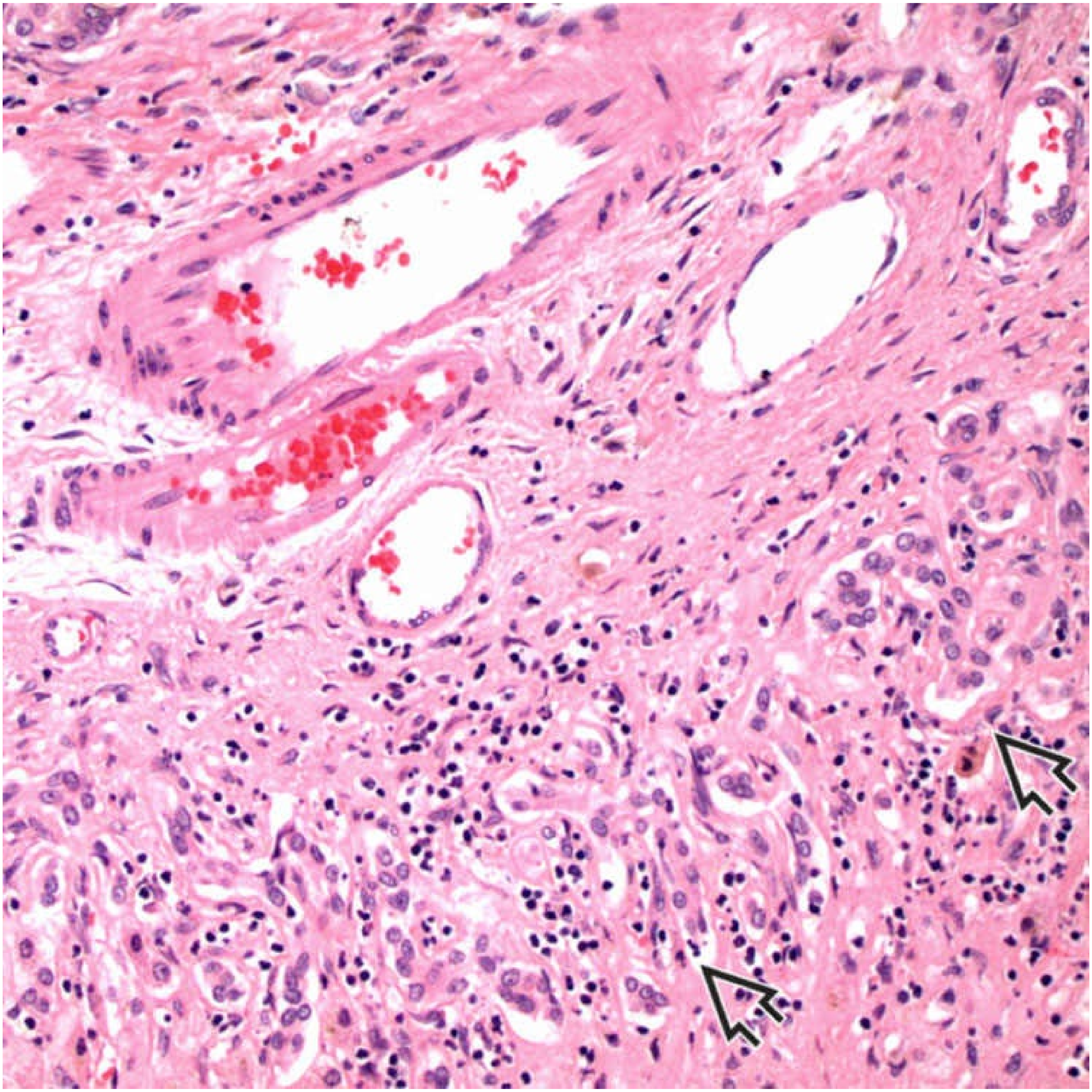


Trichrome Stain
Trichrome stain of a liver explant from a 5-year-old boy with Alagille syndrome shows micronodular cirrhosis with small, regenerative nodules separated by bands of fibrous tissue.

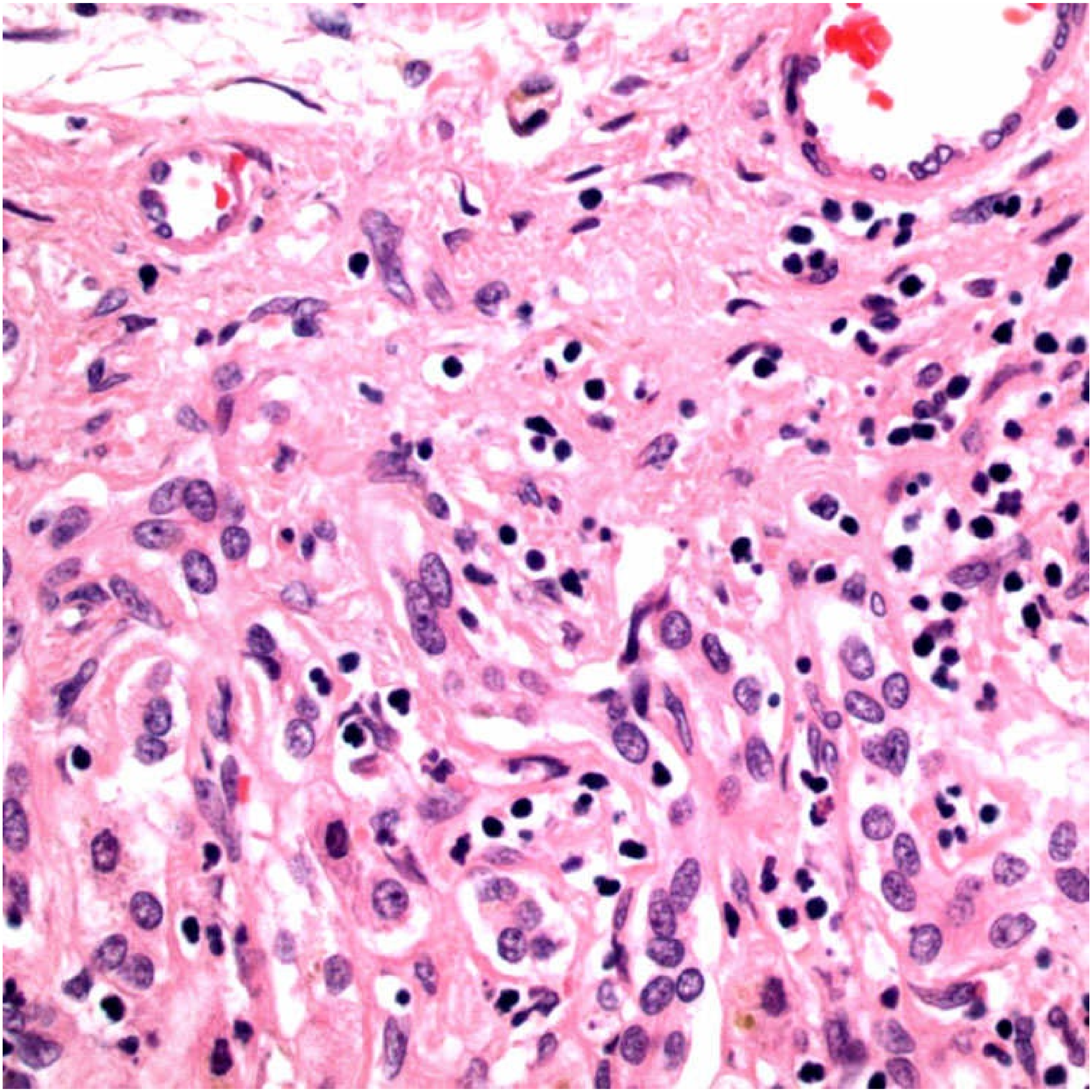


Portal Tract

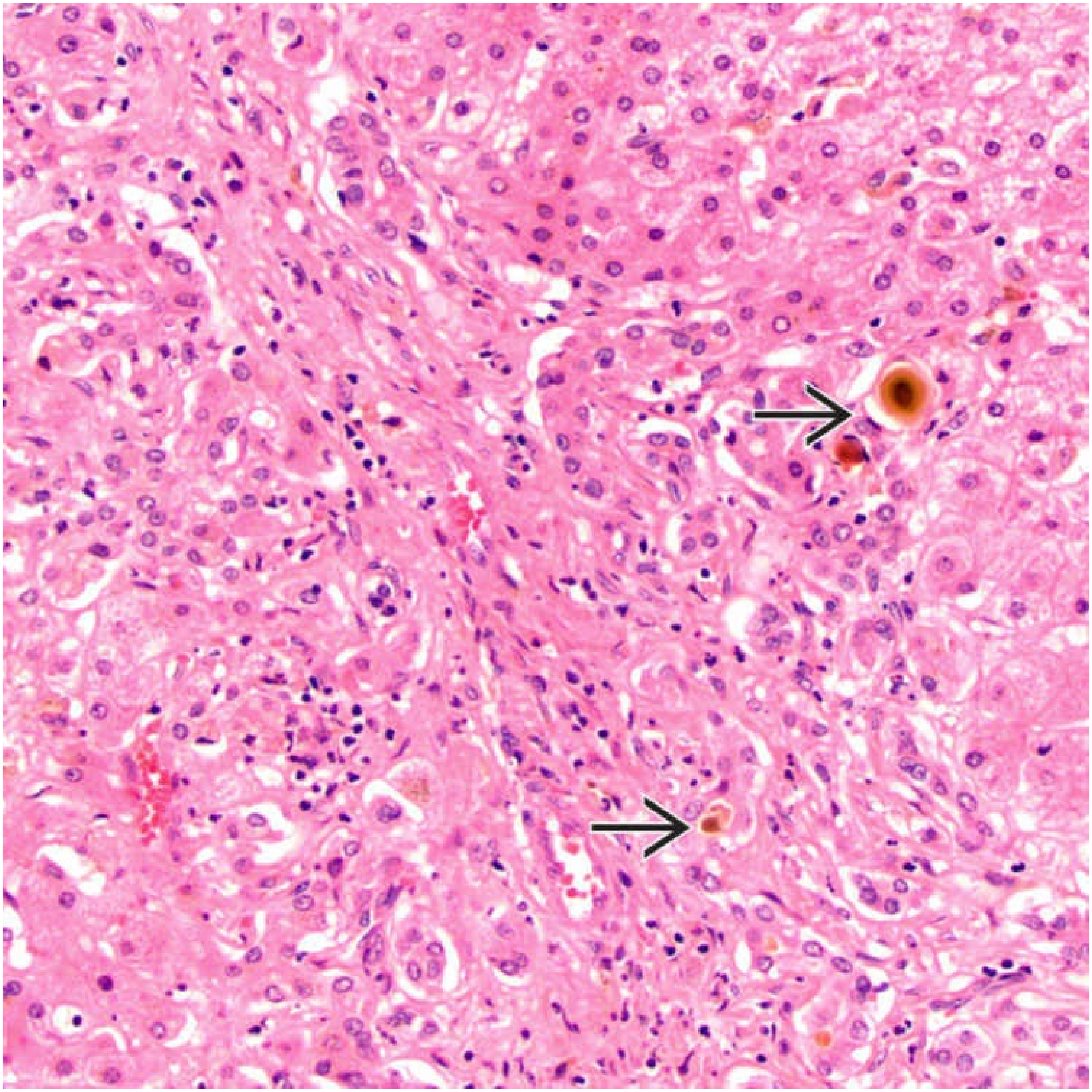
Portal tract in a child with Alagille syndrome shows an arteriole → not accompanied by a bile duct, consistent with bile duct paucity, and bile ductule reaction with inspissated bile at the portal edge ↱ .



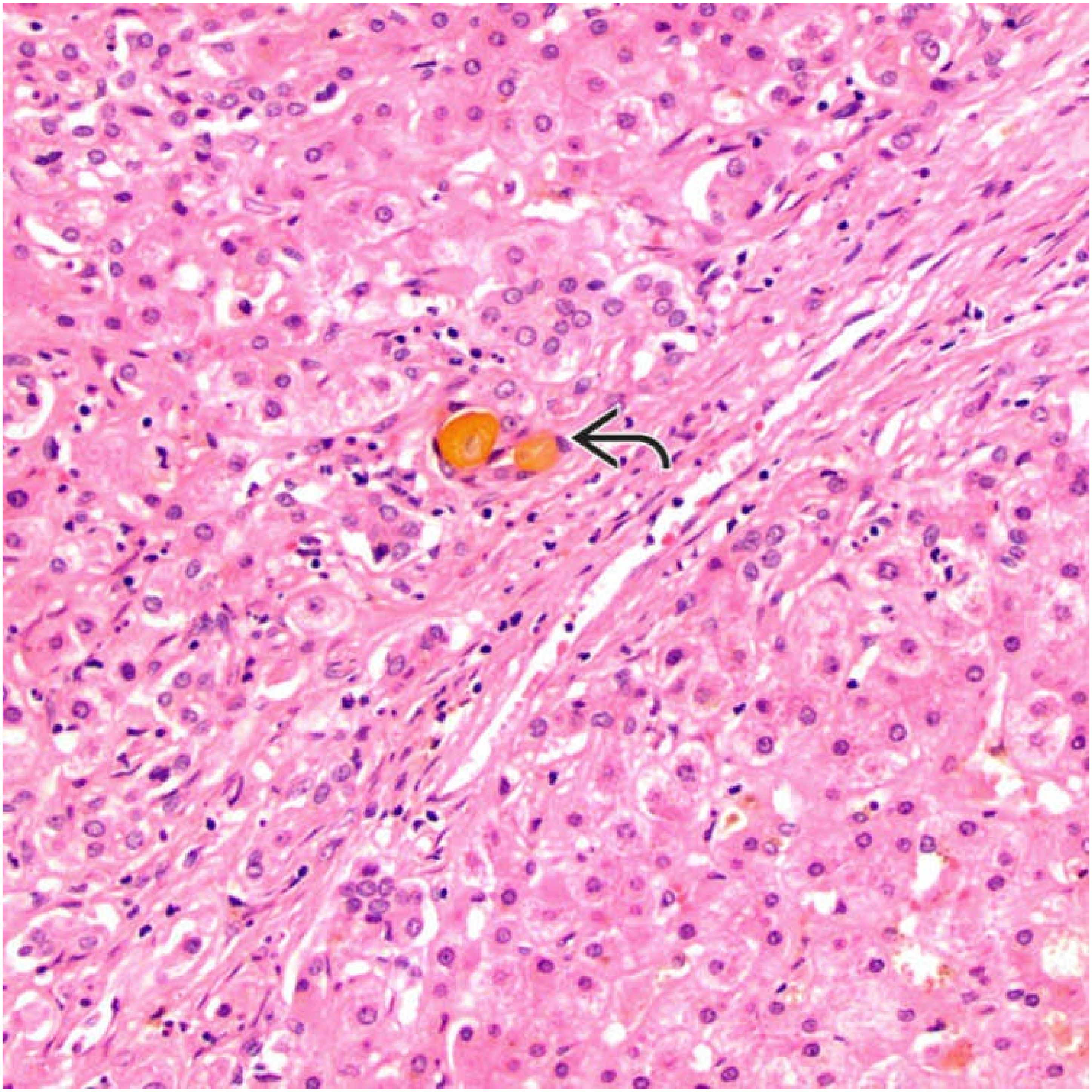
Absence of Bile Duct
The edge of a large portal area shows vascular structures (top) but no interlobular bile duct. Notice the ductular reaction at the edge of the portal area ➪ .



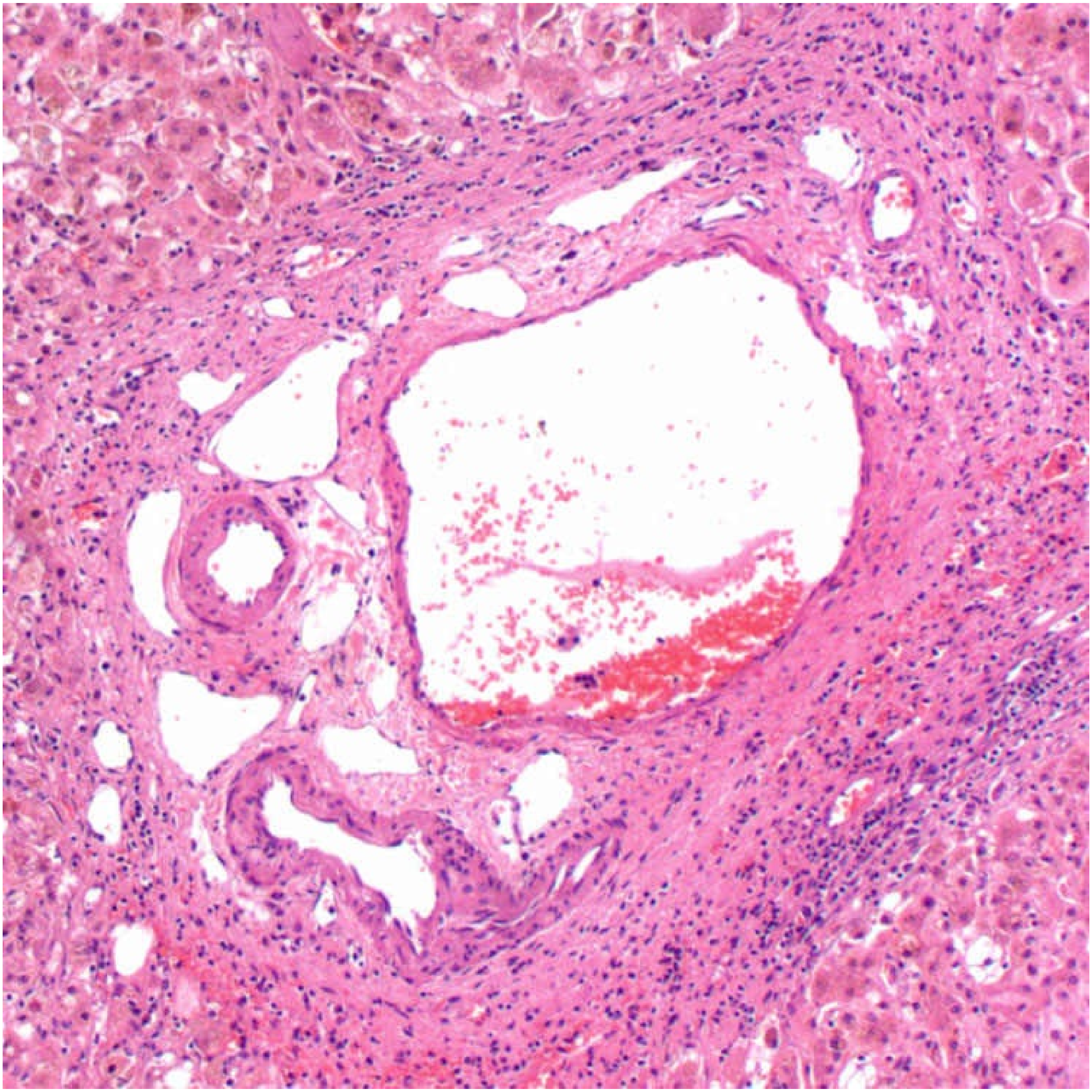
Bile Ductular Reaction
High magnification of a portal area in Alagille syndrome shows bile ductular reaction.



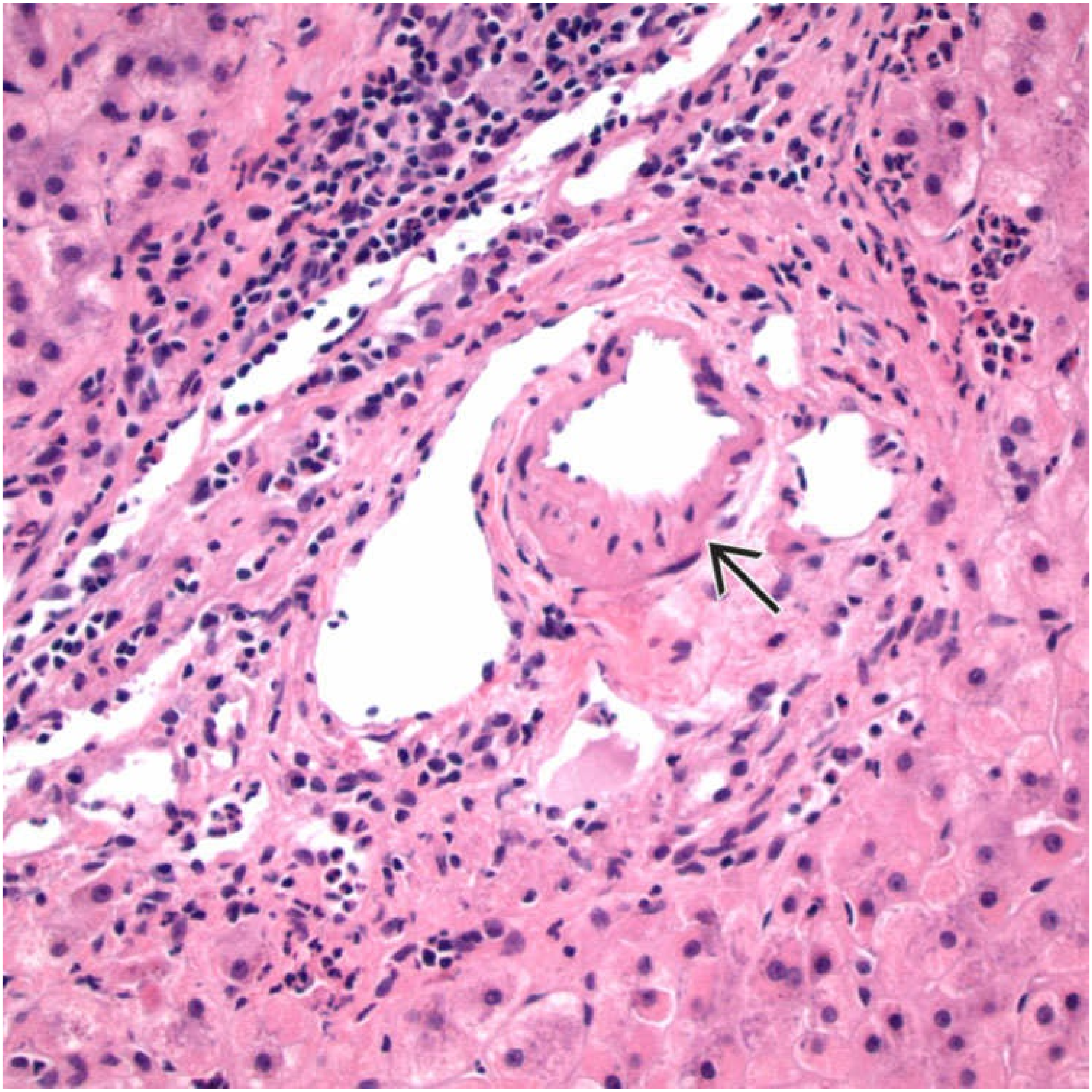
Bile Ductular Reaction
The edge of a fibrous septum in cirrhotic liver in Alagille syndrome shows bile ductular reaction with inspissated bile in bile ductules → that can lead to a misdiagnosis of extrahepatic biliary atresia.



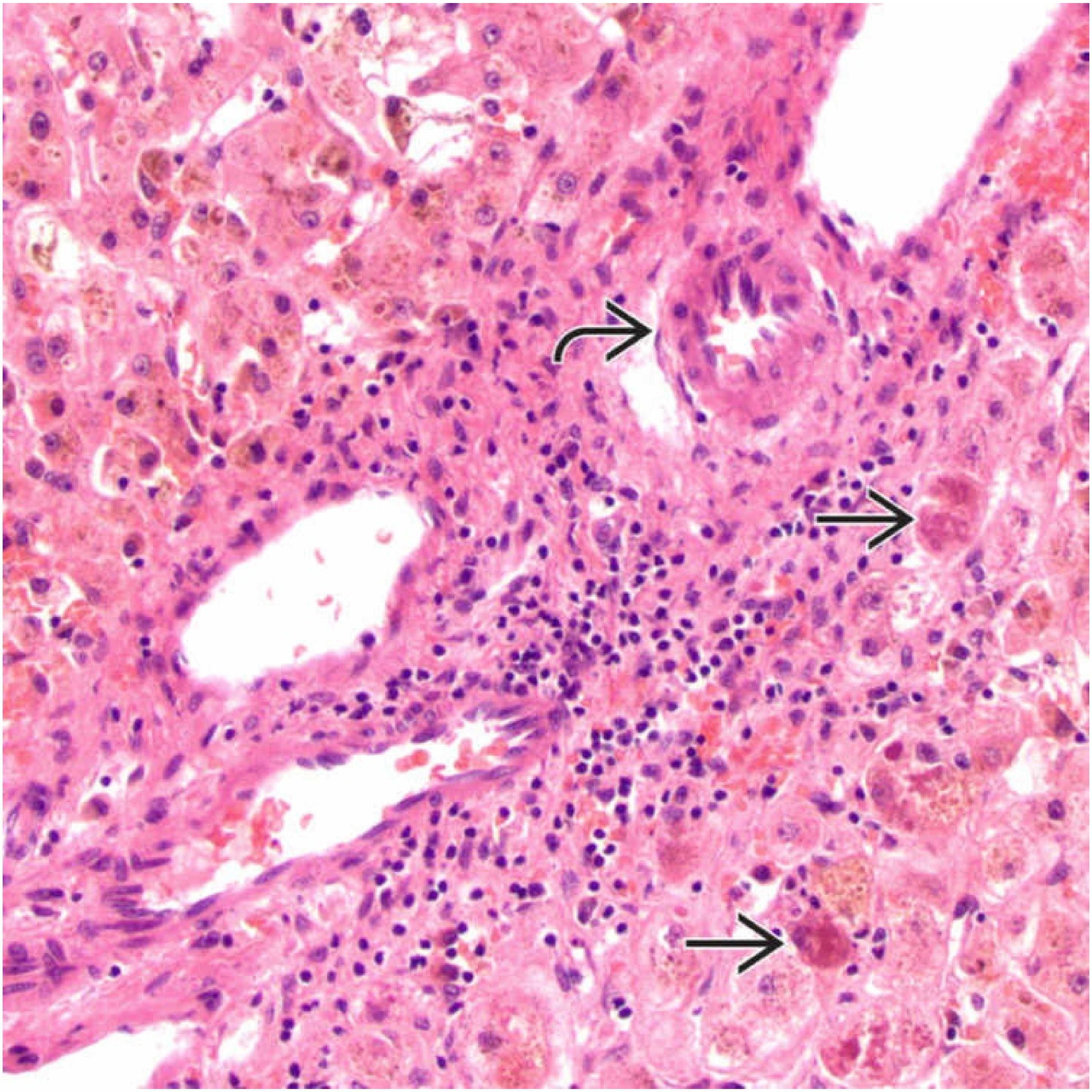
Bile Inspissated in Ductules
Bile ductular reaction in Alagille syndrome with bile inspissated in ductules ↱ can cause confusion with biliary atresia.



Vascular Structures
Large portal region in an explant from an adult patient with Alagille syndrome shows large vascular structures without bile ducts.

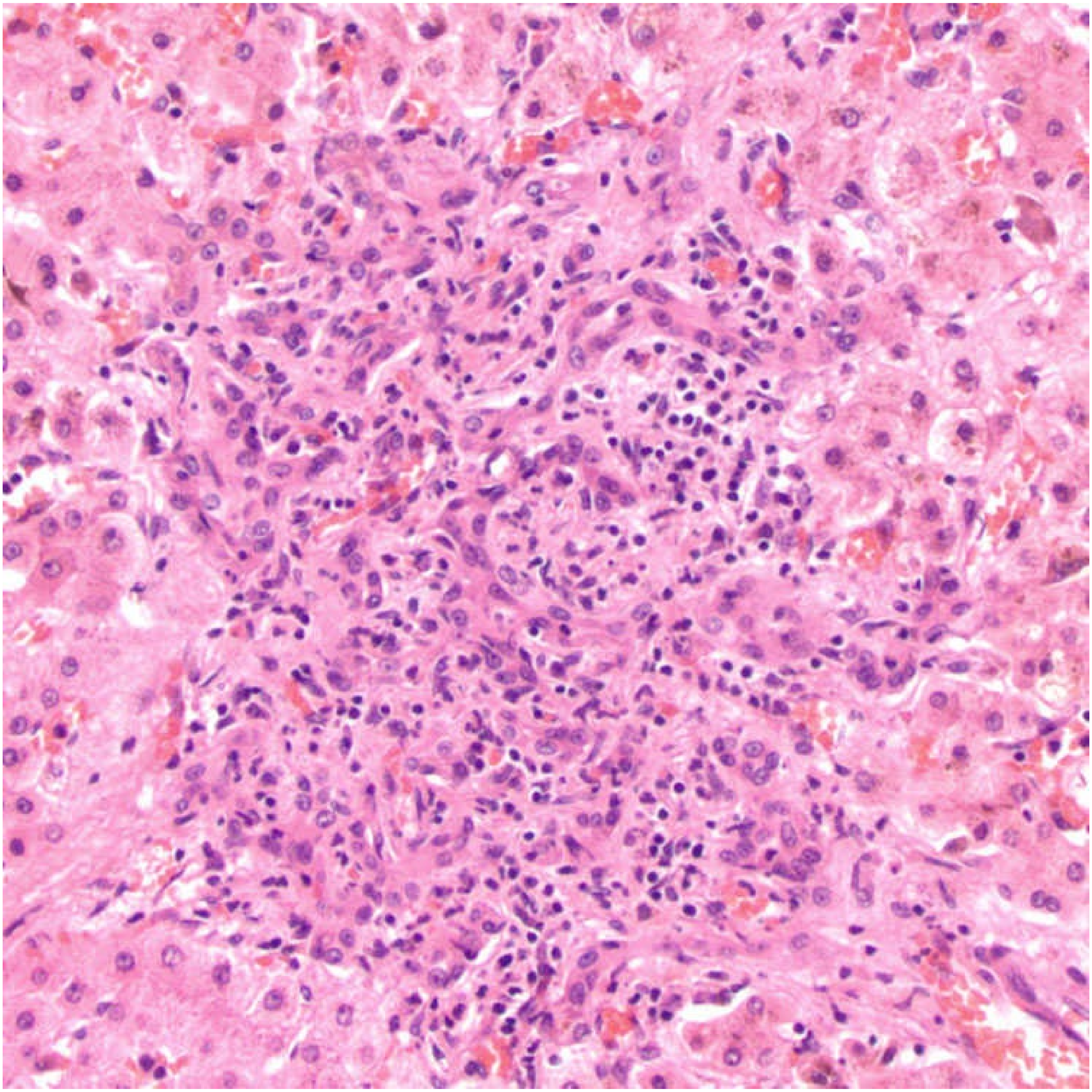


Portal Tract
Smaller portal tract in an adult patient with Alagille syndrome shows a small artery → and vein but no bile duct. Note the absence of bile ductular reaction.



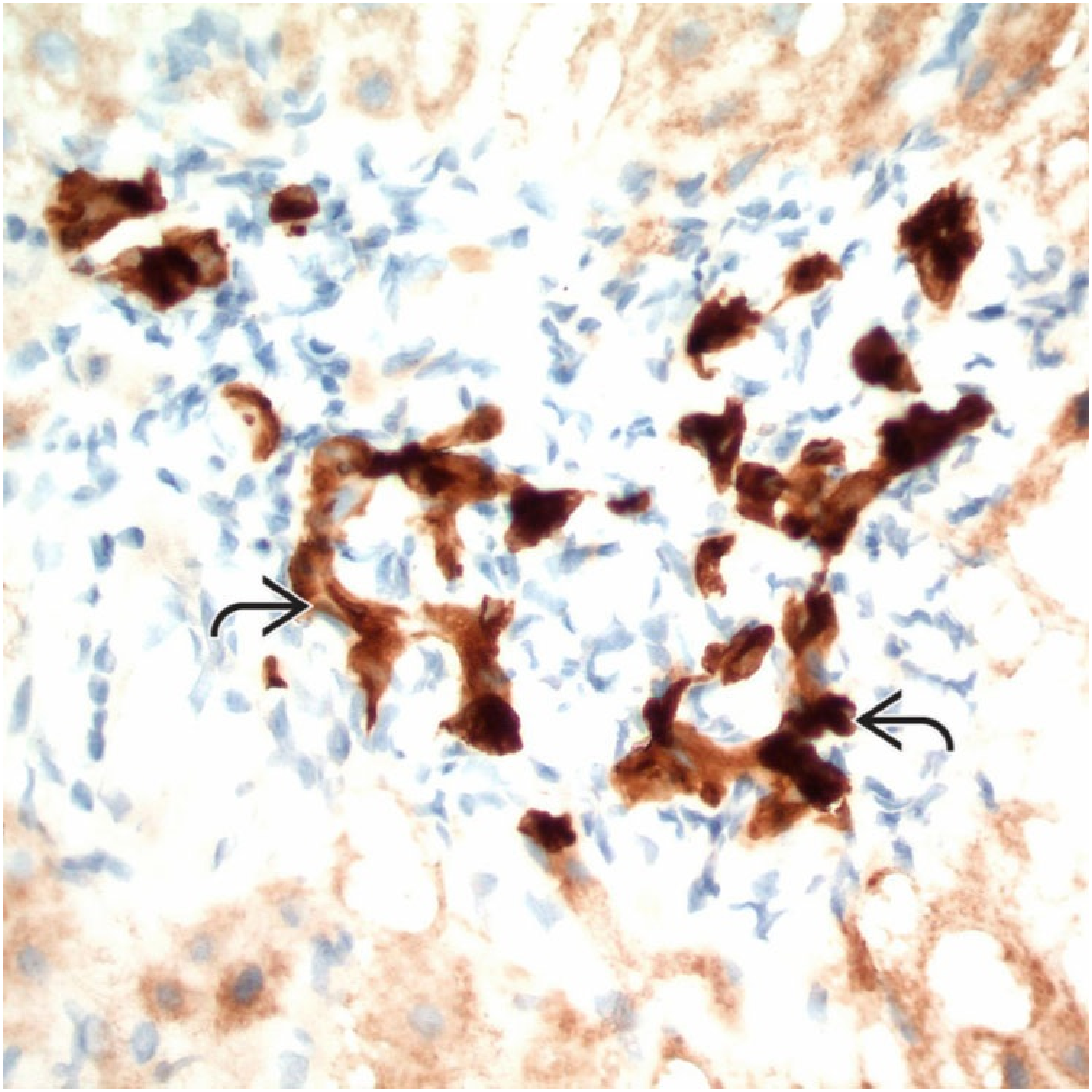
Mallory-Denk Bodies

Portal area in Alagille syndrome is shown. The surrounding liver is cholestatic with Mallory-Denk bodies →. The portal tract contains a small artery ↷ but no duct.



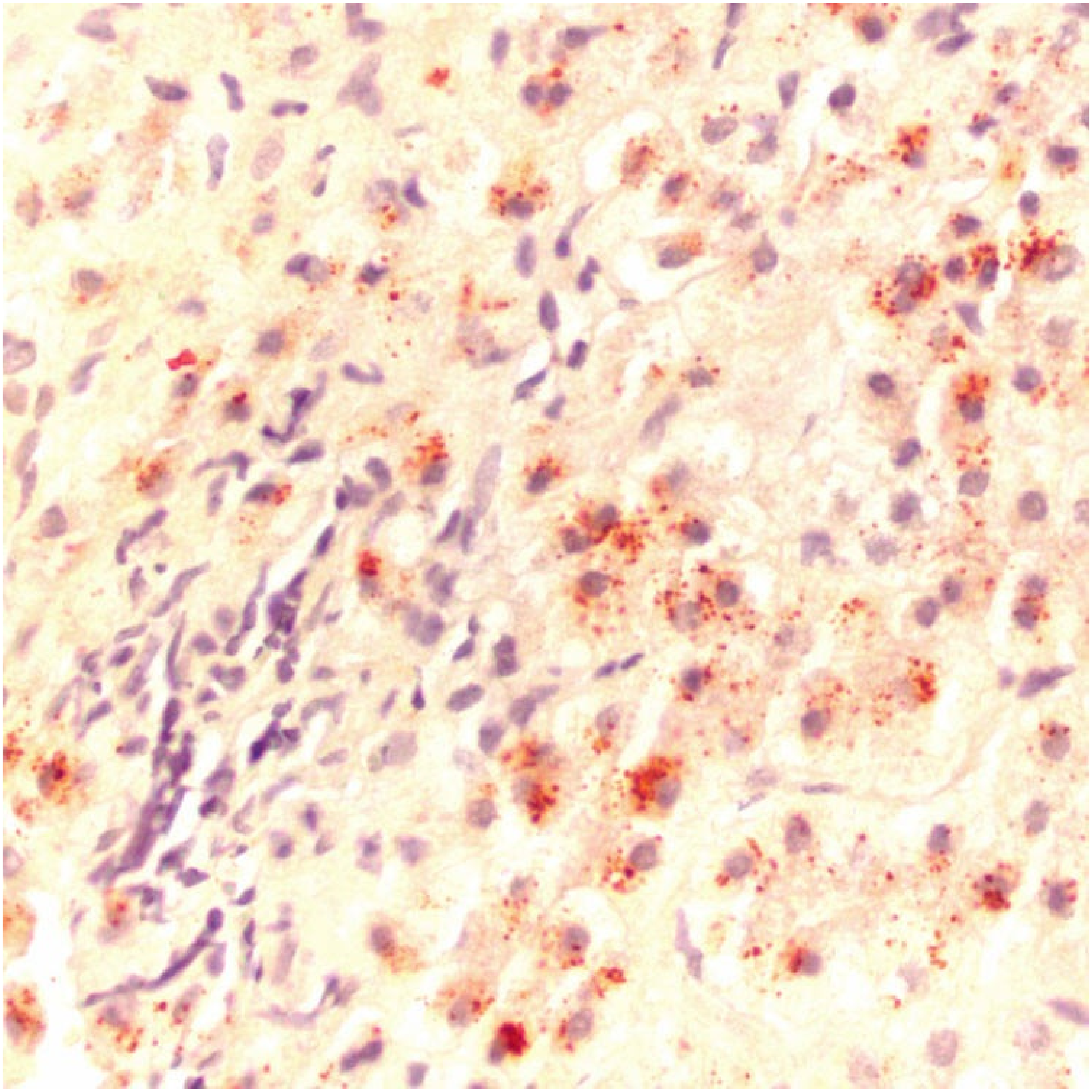
Ductular Reaction

Explanted liver in an adult patient with Alagille syndrome shows ductular reaction in a portal tract.



CK19 Stain

CK19 immunohistochemical stain in a liver biopsy from an adult patient with Alagille syndrome shows ductular reaction ↱ in a portal tract without interlobular bile duct.



Copper Stain
Copper stain in a liver biopsy from an adult patient with Alagille syndrome shows copper deposition in periportal hepatocytes (red-brown granules), consistent with chronic cholestasis.

SELECTED REFERENCES

1. Kamath, BM, et al. NOTCH2 mutations in Alagille syndrome. *J Med Genet*. 2012; 49(2):138–144.
2. Yang, H, et al. Partial external biliary diversion in children with progressive familial intrahepatic cholestasis and Alagille disease. *J Pediatr Gastroenterol Nutr*. 2009; 49(2):216–221.

3. McDaniell, R, et al. NOTCH2 mutations cause Alagille syndrome, a heterogeneous disorder of the notch signaling pathway. *Am J Hum Genet*. 2006; 79(1):169–173.
4. Bhadri, VA, et al. Hepatocellular carcinoma in children with Alagille syndrome. *J Pediatr Gastroenterol Nutr*. 2005; 41(5):676–678.
5. Kodama, Y, et al. The role of notch signaling in the development of intrahepatic bile ducts. *Gastroenterology*. 2004; 127(6):1775–1786.
6. Kamath, BM, et al. Heritable disorders of the bile ducts. *Gastroenterol Clin North Am*. 2003; 32(3):857–875. [vi].
7. McKiernan, PJ. Neonatal cholestasis. *Semin Neonatol*. 2002; 7(2):153–165.
8. Crosnier, C, et al. Alagille syndrome. The widening spectrum of arteriohepatic dysplasia. *Clin Liver Dis*. 2000; 4(4):765–778.
9. Tombaugh, TN, et al. Effects of age on the Rey-Osterrieth and Taylor complex figures: test-retest data using an intentional learning paradigm. *J Clin Exp Neuropsychol*. 1992; 14(5):647–661.

Paucity of Intrahepatic Bile Ducts (Nonsyndromic)

KEY FACTS

Terminology

- Heterogeneous group of disorders that cause bile duct paucity in patients without congenital abnormalities indicative of Alagille syndrome
- Ductopenia diagnosed when > 50% of portal tracts lack bile ducts

Etiology/Pathogenesis

- Congenital disorders: Extrahepatic biliary atresia
- Metabolic disorders: α-1-antitrypsin deficiency, cystic fibrosis, progressive familial intrahepatic cholestasis, peroxisomal disorders, disorders of bile acid synthesis, Niemann-Pick type C, arthrogryposis-renal dysfunction cholestasis
- Chromosomal abnormalities: Turner syndrome, monosomy X, trisomies
- Intrauterine infections: CMV, rubella, syphilis
- Idiopathic: Diagnosis of exclusion

Clinical Issues

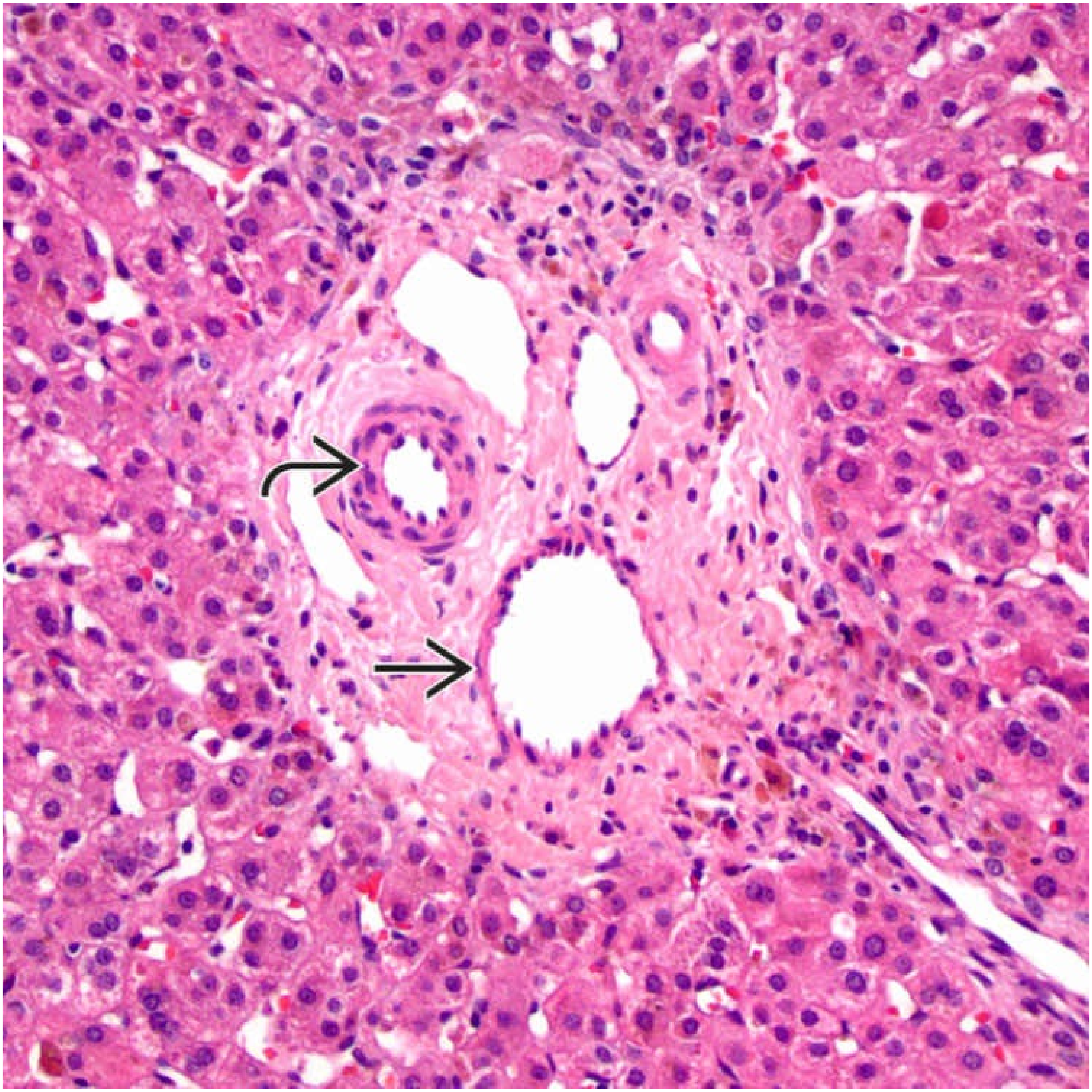
- Prognosis varies depending on underlying cause and ranges from liver failure to complete resolution
- Treated with ursodeoxycholic acid and drugs to combat pruritus
- ~ 45% progress to cirrhosis, requiring liver transplantation

Microscopic

- Native bile ducts absent in > 1/2 of portal tracts
- Intracellular cholestasis and giant cell transformation of hepatocytes
- Fibrosis ranging from portal fibrosis to cirrhosis

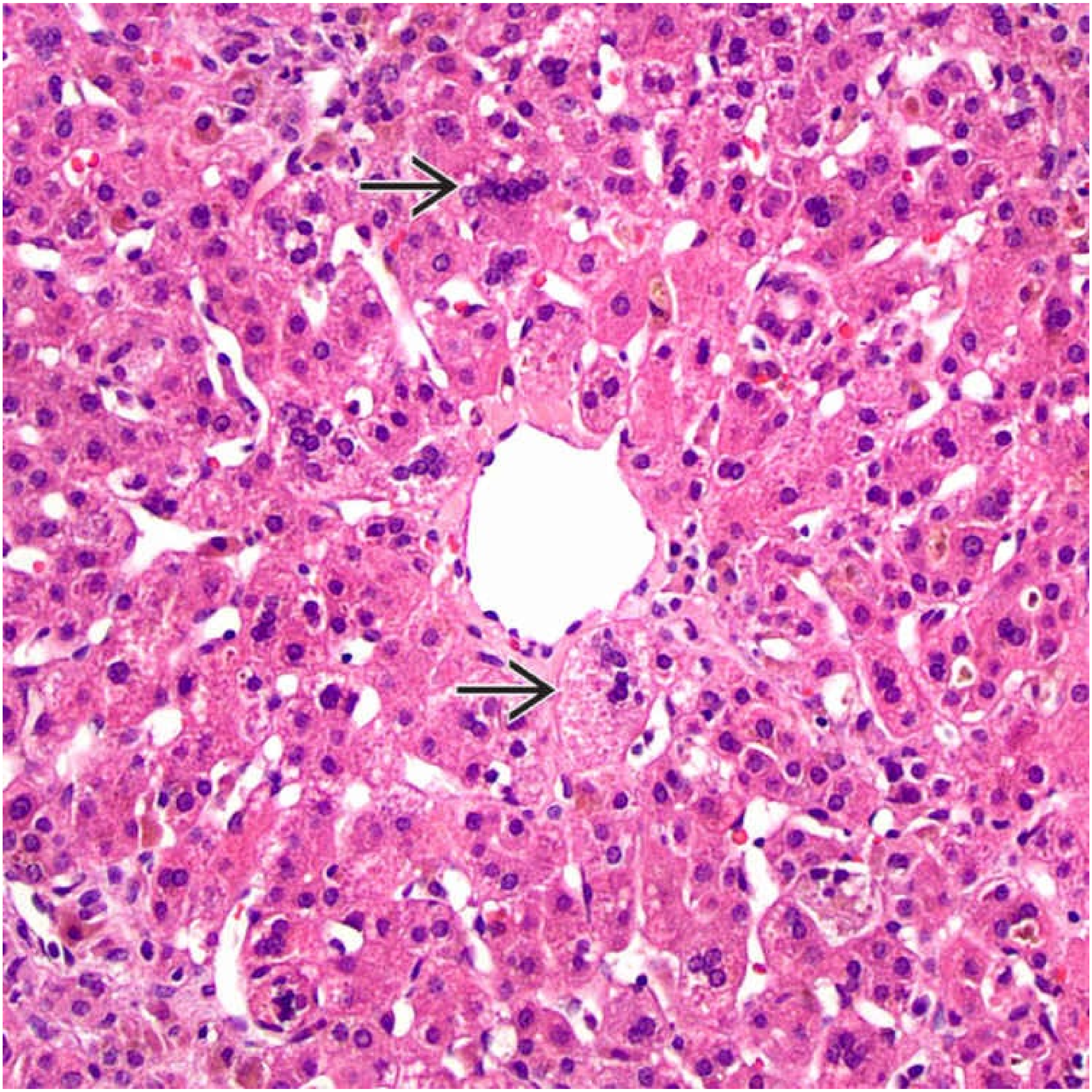
Top Differential Diagnoses

• Paucity of intrahepatic bile ducts (syndromic)
• Extrahepatic biliary atresia
• α-1-antitrypsin deficiency
• Cystic fibrosis
• Progressive familial intrahepatic cholestasis

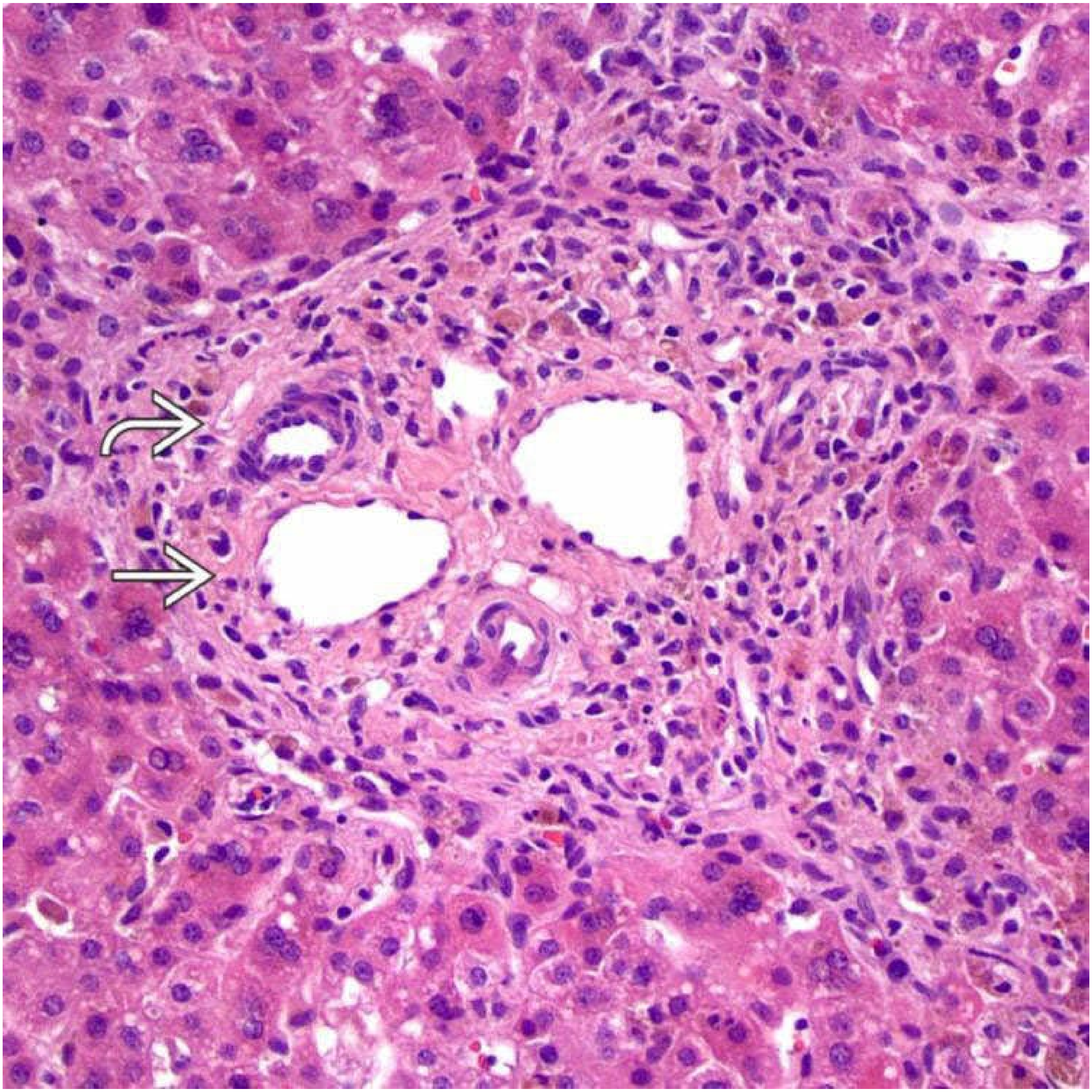


Portal Tract

A portal tract in an infant with nonsyndromic paucity of intrahepatic bile ducts shows arteries ↷ and veins → but no bile ducts. The hepatocytes are compact and clustered.

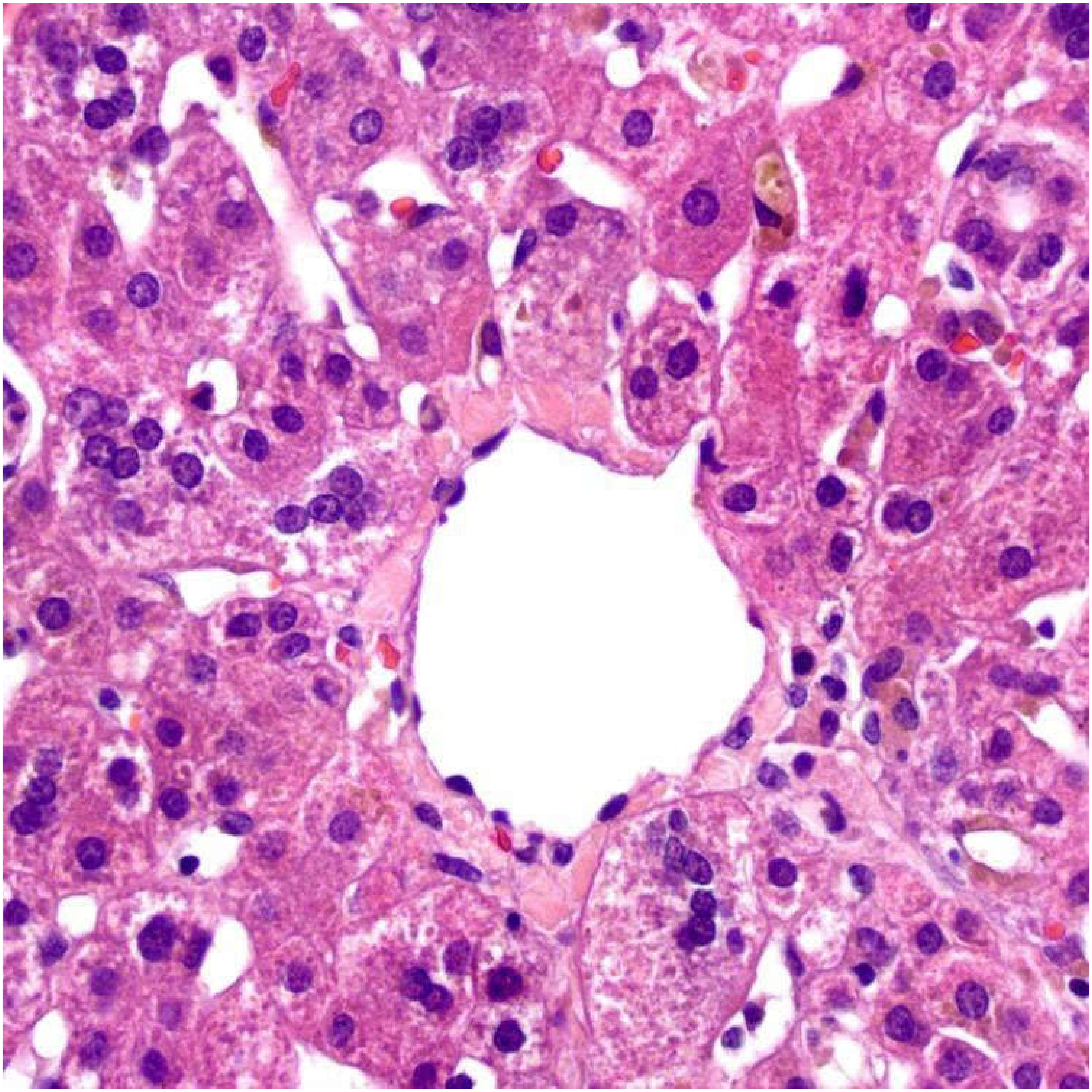


Centrilobular Region
The centrilobular region in nonsyndromic bile duct paucity shows cholestasis and giant cell transformation of hepatocytes →, nonspecific features of many neonatal cholestatic disorders.



Portal Tract

Another portal tract in an infant with nonsyndromic paucity of intrahepatic bile ducts shows arteries and veins but no bile ducts. The hepatocytes are compact and clustered.



Higher Magnification

Higher magnification of the centrilobular region in nonsyndromic bile duct paucity shows cholestasis and giant cell transformation of hepatocytes, nonspecific features of many neonatal cholestatic disorders.

TERMINOLOGY

Synonyms

- Hypoplasia of intrahepatic bile ducts
- Intrahepatic biliary atresia

Definitions

- Heterogeneous group of disorders that cause bile duct paucity or ductopenia in patients without congenital abnormalities indicative of Alagille syndrome
  - Ductopenia defined as significant decrease in number of interlobular bile ducts
    - Ratio of number of interlobular bile ducts to number of portal tracts is < 0.4, with normal between 0.9 and 1.8
    - Alternatively, ductopenia is diagnosed when > 50% of portal tracts lack bile ducts; normally, 80-100% of portal tracts contain ducts

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Congenital disorders: Extrahepatic biliary atresia
- Metabolic disorders: α-1-antitrypsin deficiency, cystic fibrosis, progressive familial intrahepatic cholestasis, peroxisomal disorders, disorders of bile acid synthesis, Niemann-Pick type C, arthrogryposis-renal dysfunction-cholestasis syndrome
- Chromosomal abnormalities: Turner syndrome, monosomy X, trisomies

Infectious Agents

- Intrauterine infections: CMV, rubella, syphilis

Idiopathic

- Accounts for variable percentage of total cases, depending on population studied
- Prevalence has been diminishing as metabolic and genetic mechanisms of ductopenia are elucidated
- Diagnosis of exclusion

CLINICAL ISSUES

Epidemiology

- Incidence
  - Varies in population studied but increased in regions where consanguineous marriage is common
- Age
  - Generally considered disease of childhood as adults with ductopenia are classified in different categories
  - Some patients with idiopathic adulthood ductopenia may represent late presentation of disorder

Presentation

- Jaundice and acholic stools
- Pruritus
- Hepatomegaly

Laboratory Tests

- Increased alkaline phosphatase, γ-glutamyl transpeptidase, and serum bilirubin
- Increased serum cholesterol may be seen

Natural History

- Complications of fat malabsorption and deficiency of fat-soluble vitamins
  - Prolonged prothrombin time, rickets, vitamin E-responsive hemolytic anemia, corneal ulcers

Treatment

- Surgical approaches
  - Liver transplantation may be necessary for patients who progress to cirrhosis and liver failure
- Drugs
  - Ursodeoxycholic acid, cholestyramine, phenobarbital

Prognosis

- Ranges from liver failure requiring transplant to complete resolution, depending on underlying cause
  - Progression to cirrhosis seen in ~ 45% of patients
- Prognosis worse than for patients with syndromic paucity of intrahepatic bile ducts
- Many patients die of progressive liver failure without transplantation

MICROSCOPIC

Histologic Features

- Interlobular bile ducts absent in > 1/2 of portal tracts
  - Ductular reaction may be present and may hinder evaluation of duct loss
  - To reliably determine ductopenia, at least 10 portal tracts must be evaluated
- Intracellular cholestasis and giant cell transformation of hepatocytes
- Fibrosis is variable, ranging from mild portal fibrosis to cirrhosis

DIFFERENTIAL DIAGNOSIS

Paucity of Intrahepatic Bile Ducts (Syndromic)

- Presence of congenital abnormalities indicative of Alagille syndrome
  - Including skeletal, ocular, and cardiac abnormalities, and characteristic facies
- *JAG1* mutations

Extrahepatic Biliary Atresia

- Hepatobiliary scanning shows absent common bile duct
- Ultrasound shows absent or small gallbladder

- Liver biopsy shows ductular reaction with bile plugs in cholangioles

α-1-Antitrypsin Deficiency

- PAS-diastase globules in hepatocytes often present although may be absent in early life
- Proteinase inhibitor phenotyping, measurement of serum α-1-antitrypsin

Cystic Fibrosis

- Bile duct reaction with PAS(+) inspissated secretion in duct lumen

Progressive Familial Intrahepatic Cholestasis

- Identification of genetic mutation, immunohistochemistry for deficiency of responsible canalicular protein

Adulthood Idiopathic Ductopenia

- Ductopenia in adult without specific disease that results in ductopenia
- May be same disorder as childhood nonsyndromic paucity of intrahepatic bile ducts

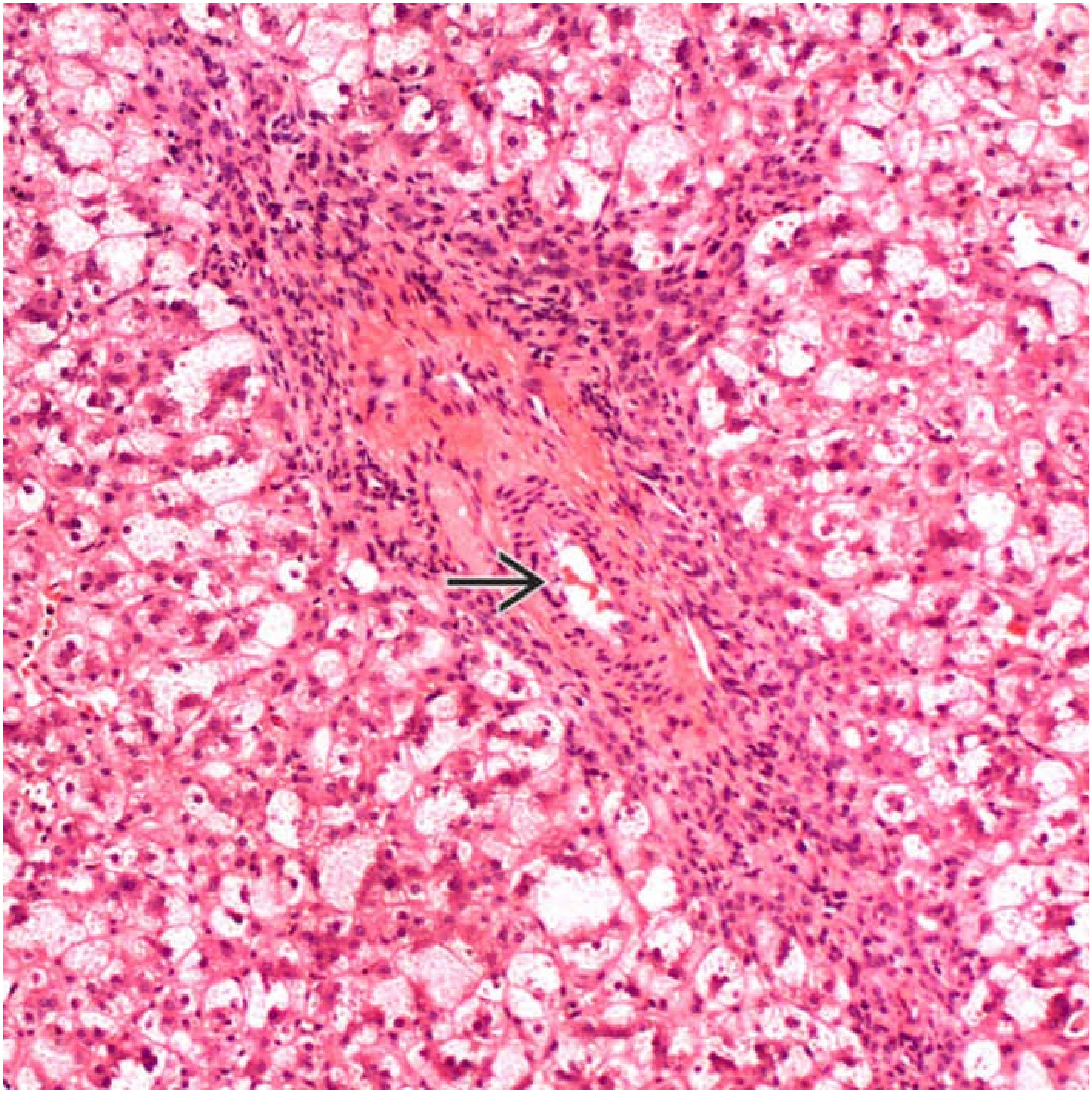
Peroxisomal Disorder (Zellweger Syndrome)

- Reduced or absent peroxisomes on ultrastructural examination
- Accumulation of very long chain fatty acids, phytanic acid, L-pipecolic acid, bile acid intermediates

DIAGNOSTIC CHECKLIST

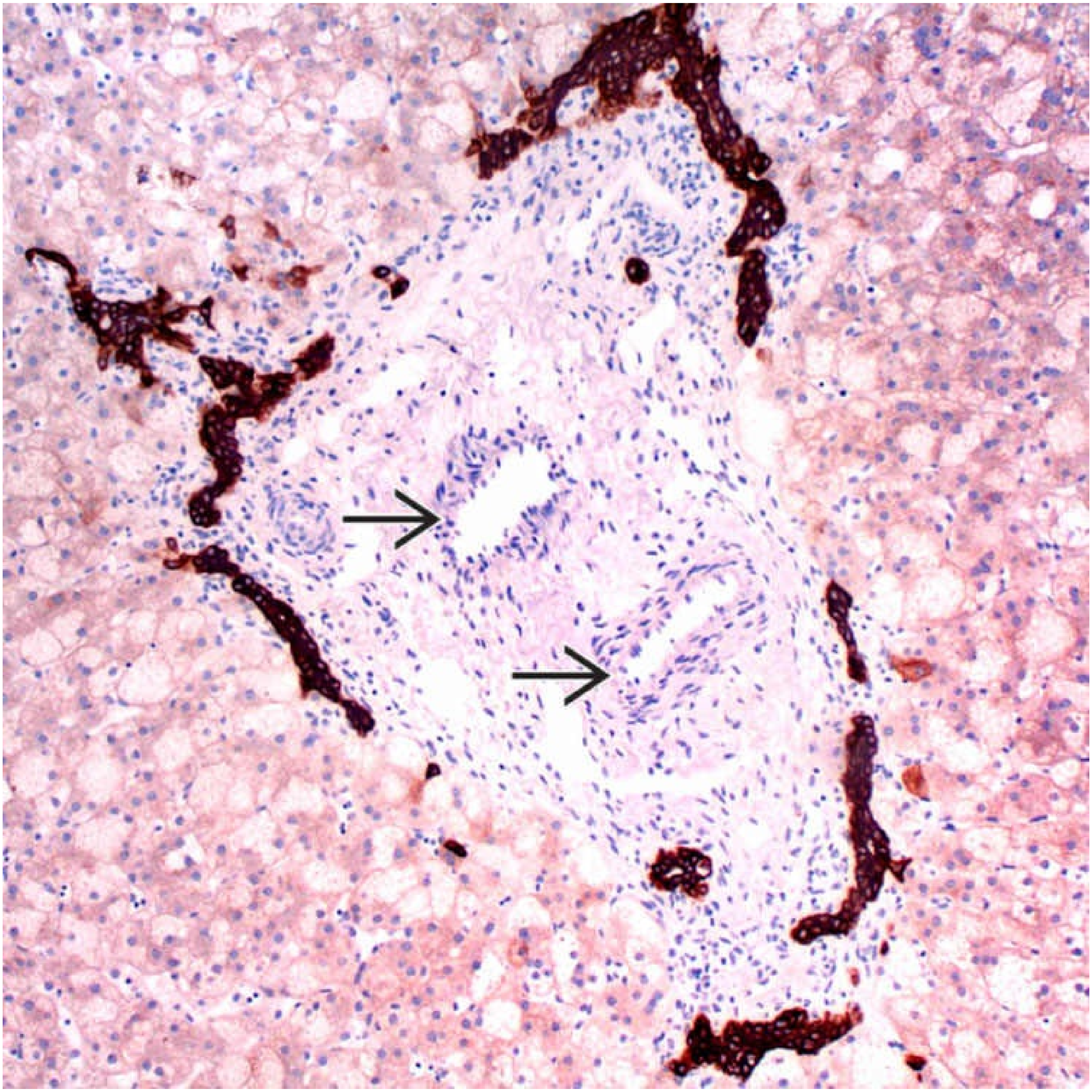
Clinically Relevant Pathologic Features

- As peripheral bile ducts are last to undergo remodeling, biopsies from premature infants or even superficial biopsies from near-term infants can give false impression of paucity

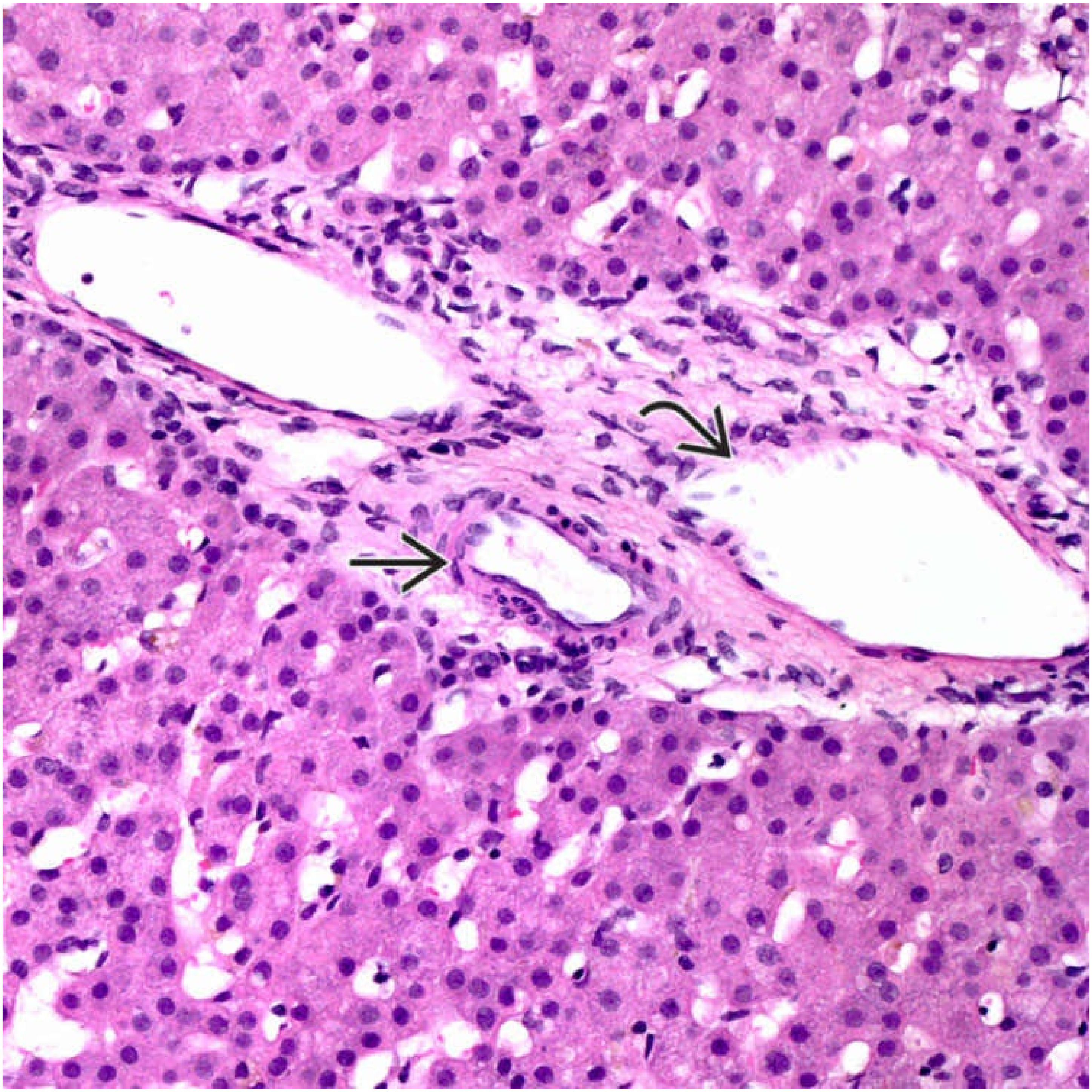


Portal Tract

A portal tract in an infant with ductopenia shows a muscular artery → without an accompanying bile duct. Ductular reaction is evident at the portal edge. The hepatocytes show giant cell transformation.

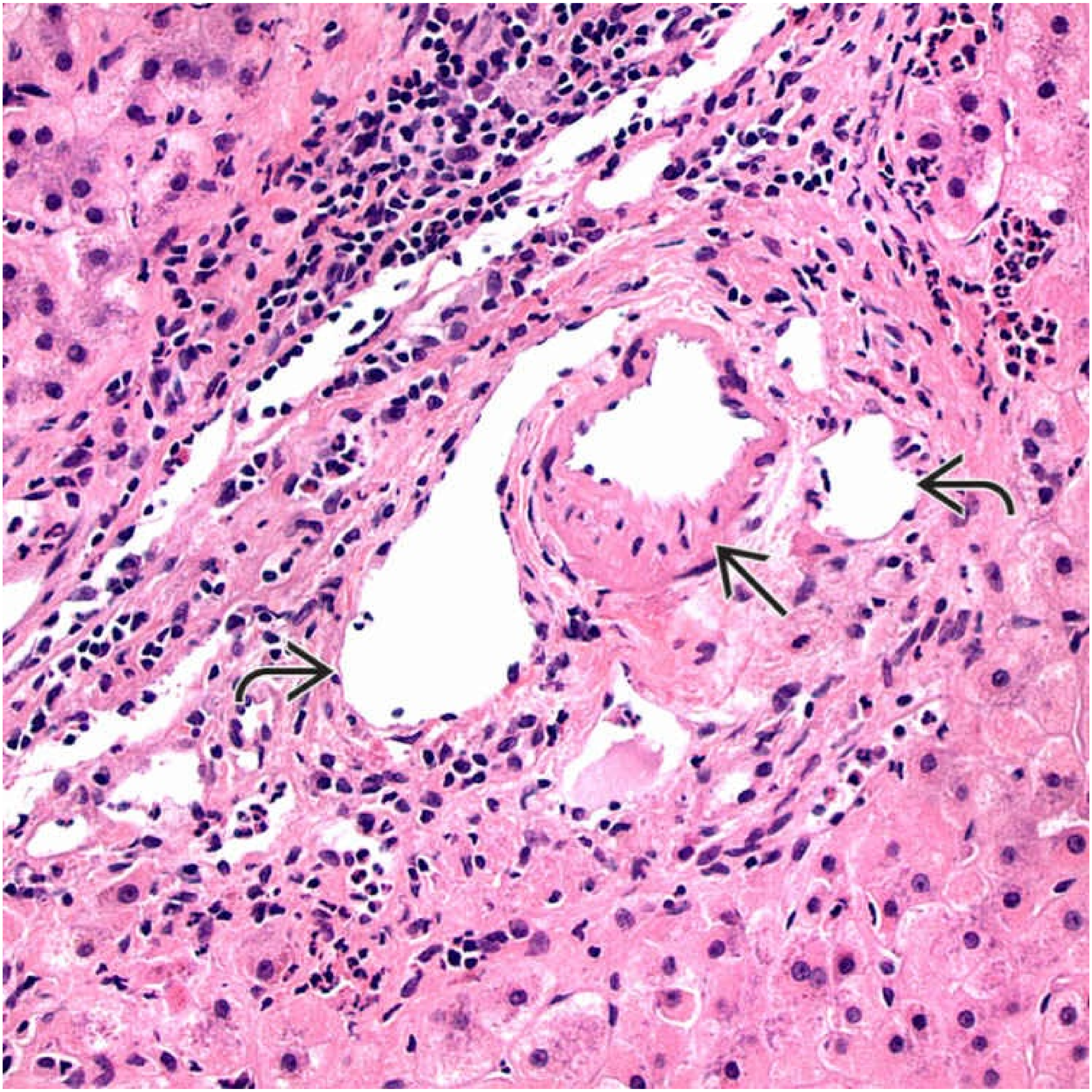


CK19 Stain
CK19 immunohistochemical stain shows peripheral ductules surrounding this portal tract, reminiscent here of ductal plate malformation, but the muscular arteries in the center of the portal tract → lack a similarly sized accompanying bile duct.



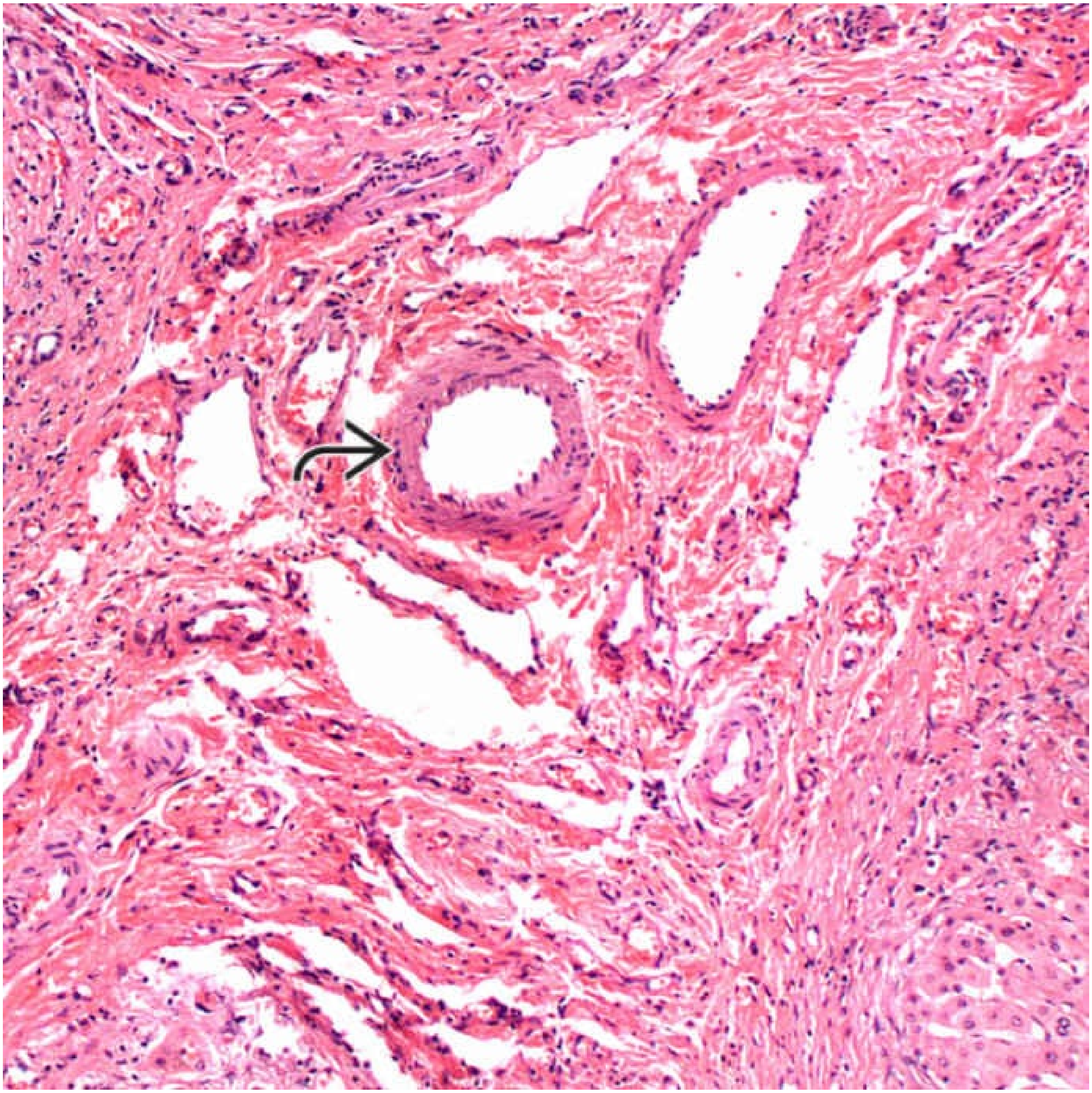
Portal Tract

A portal tract in an infant carrying a diagnosis of progressive familial intrahepatic cholestasis shows arteries and veins but no bile duct.



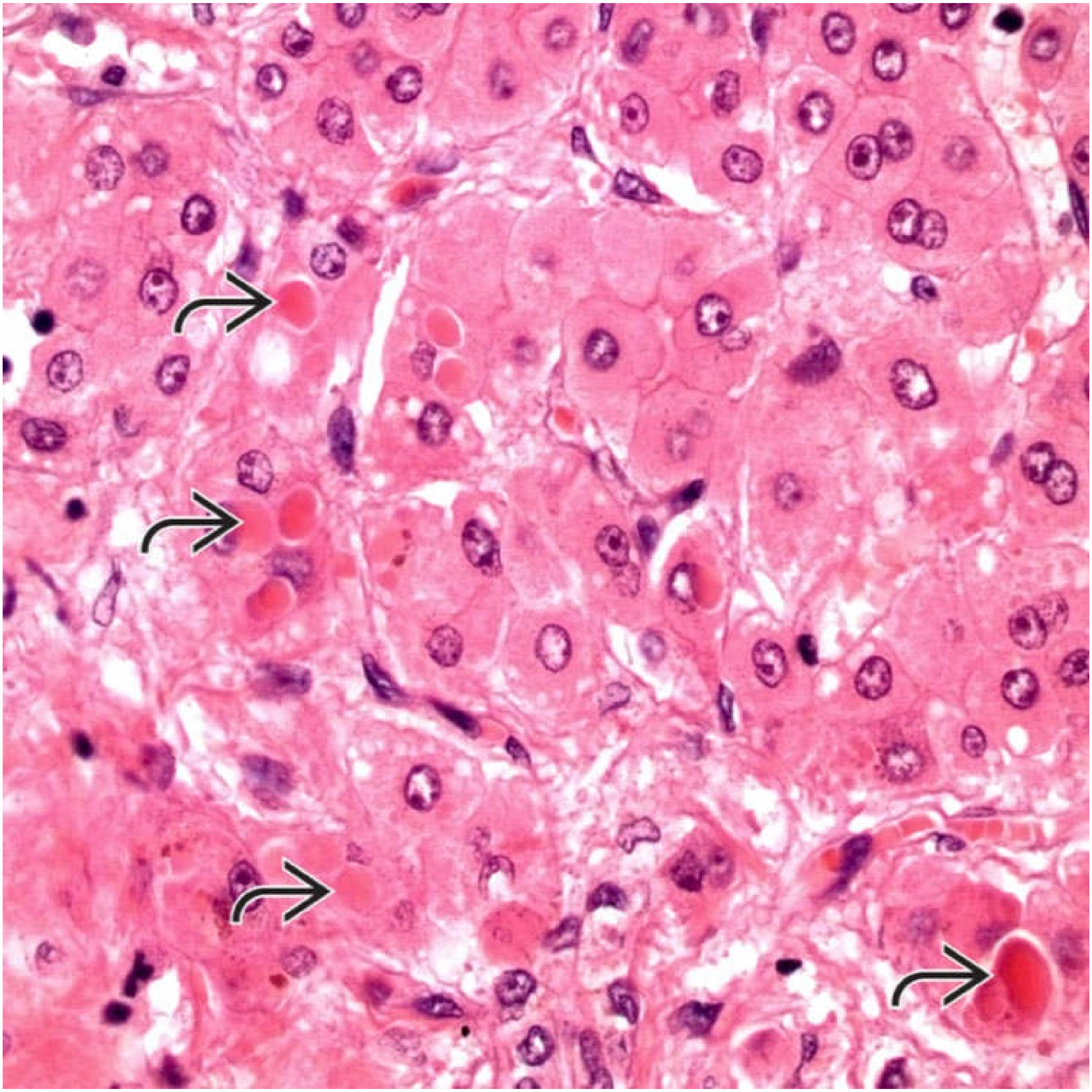
Portal Tract

A portal tract in an infant with syndromic bile duct paucity (Alagille syndrome) shows an artery → and veins ↱ but no bile duct. There is also a mild portal lymphocytic infiltrate.



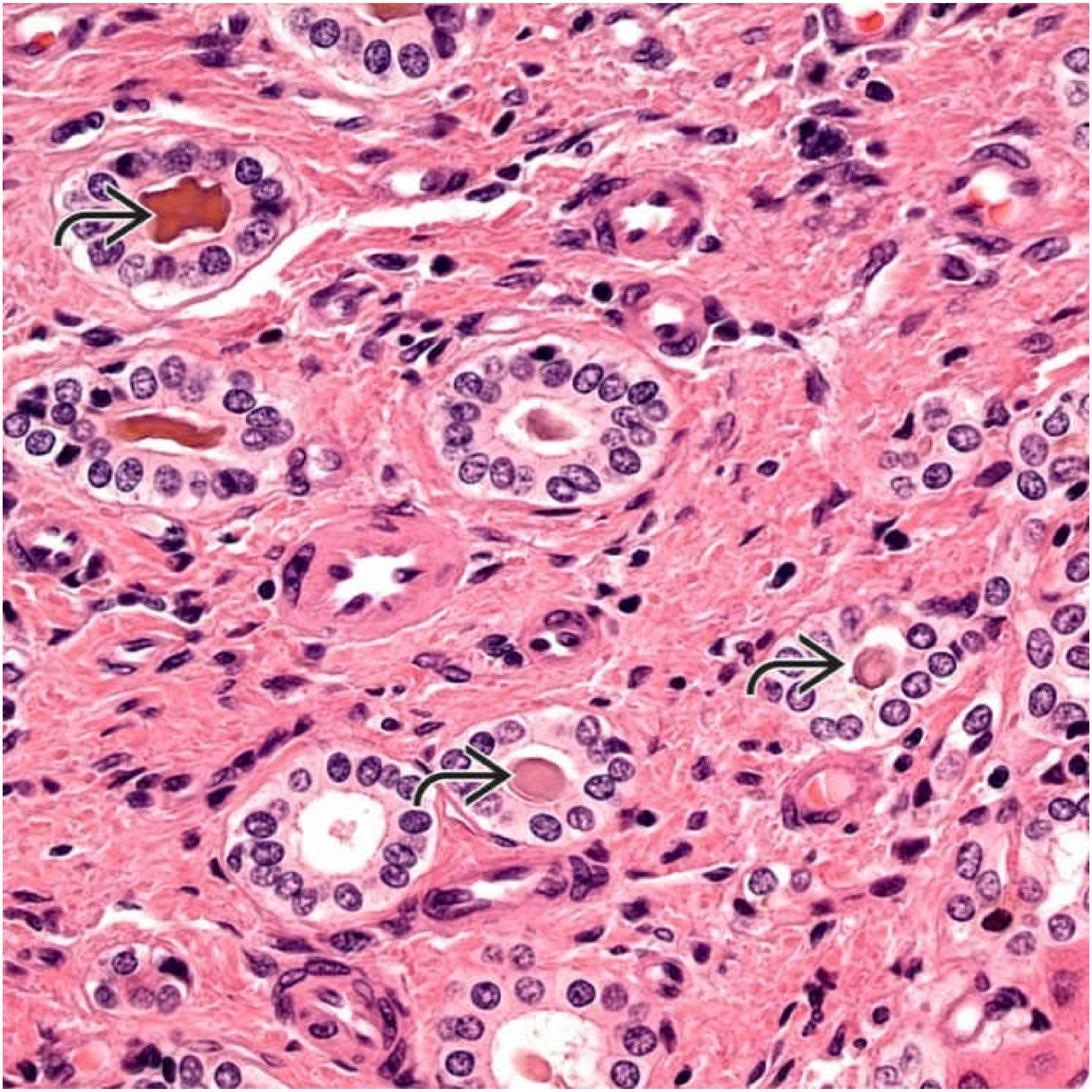
Vascular Structures

A large portal area in an explant from a child with α-1-antitrypsin deficiency shows several vascular structures including a medium-sized muscular artery, but no bile duct.



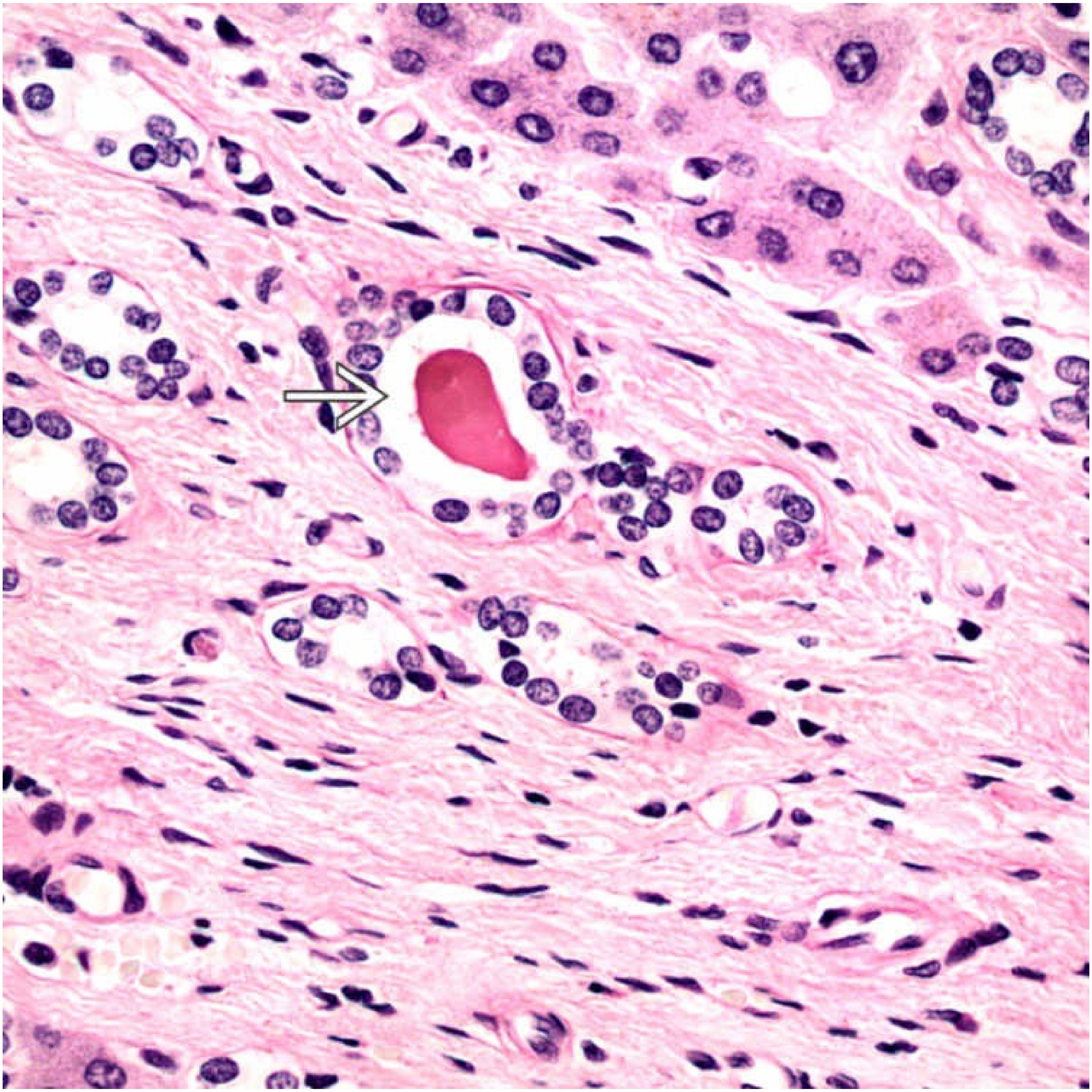
Cytoplasmic Globules

High-power examination of the liver in a child with α-1-antitrypsin deficiency shows eosinophilic globules in periseptal hepatocytes ↱ consistent with abnormal accumulation of α-1-antitrypsin.

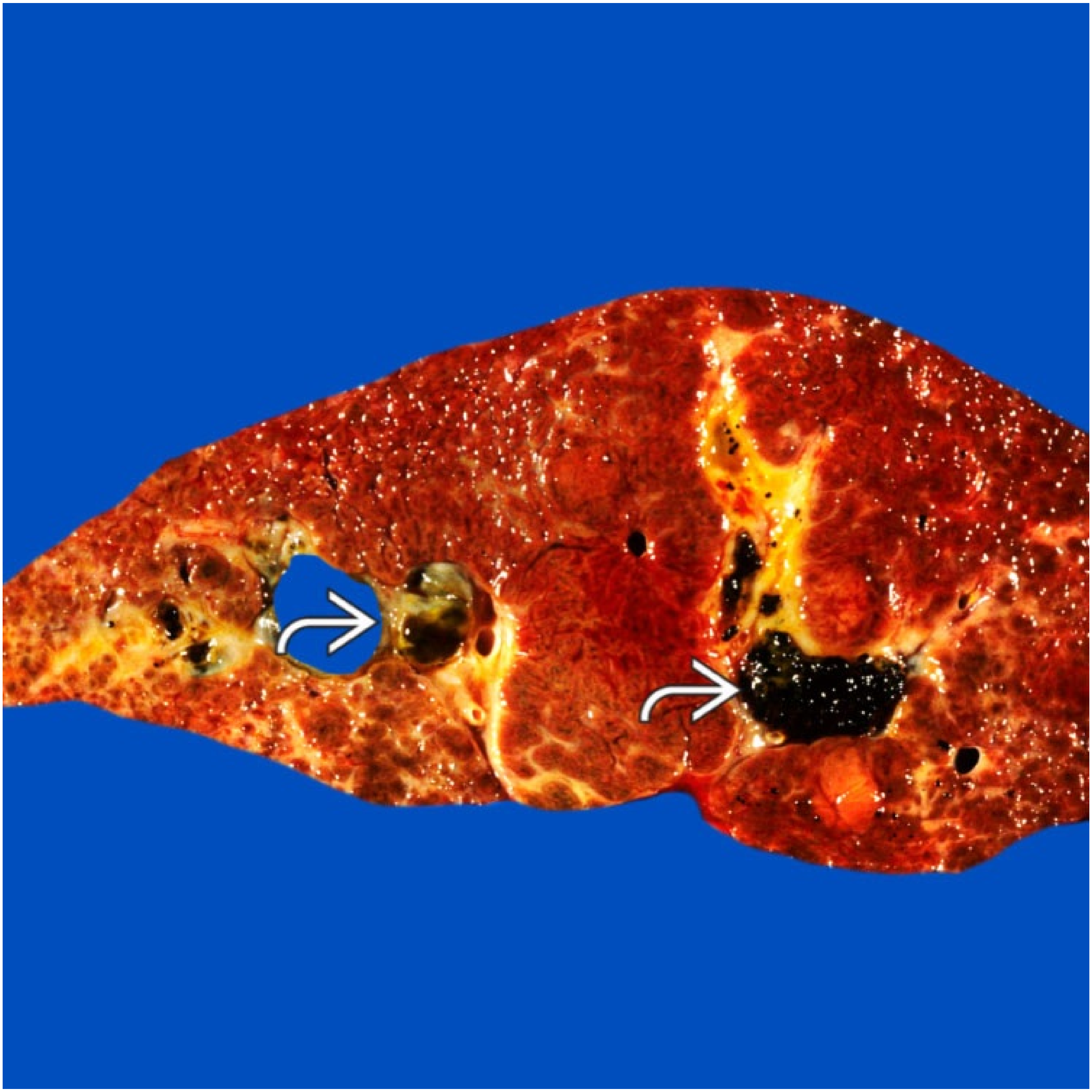


Cystic Fibrosis

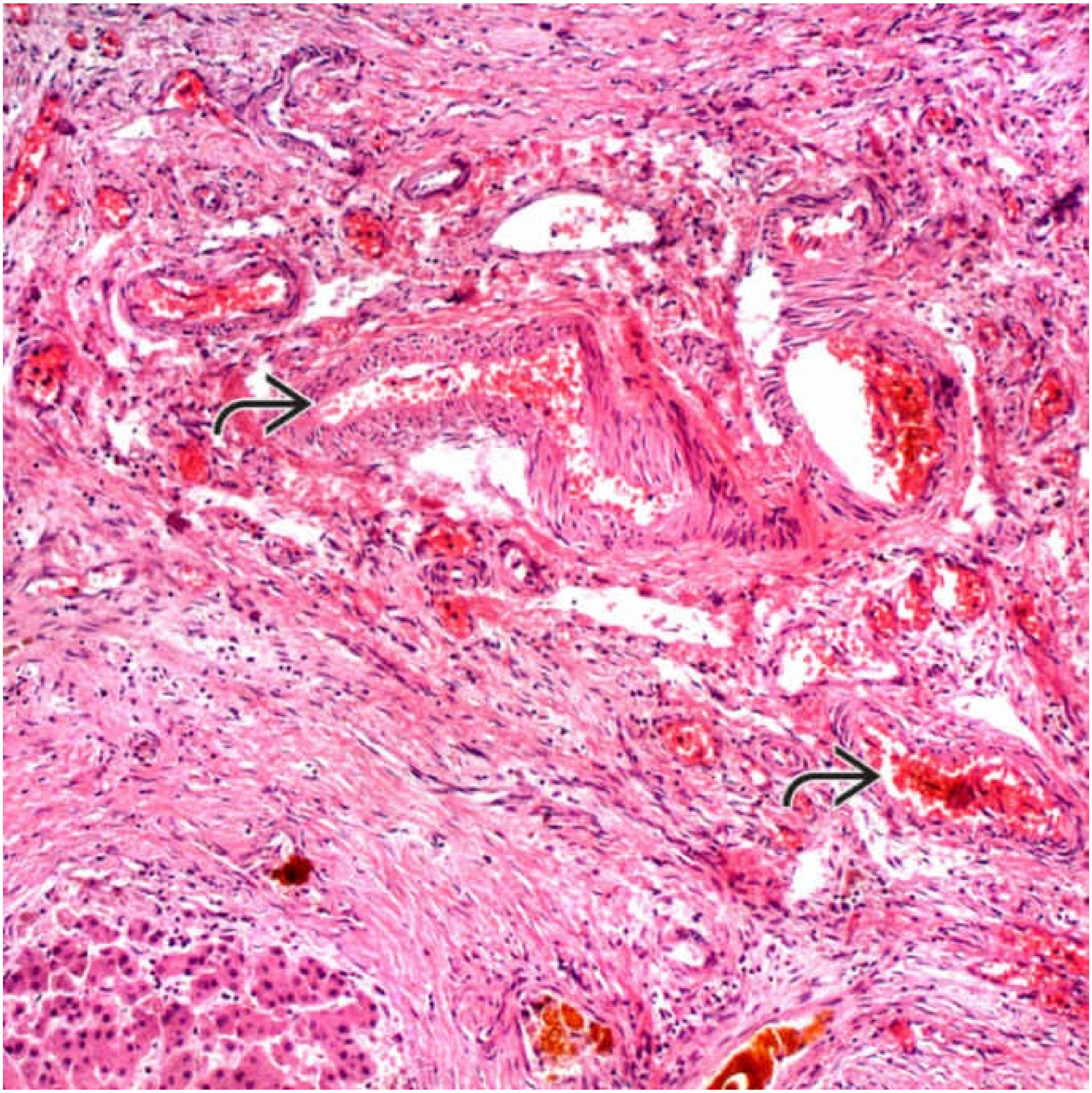
Cystic fibrosis can lead to ductopenia secondary to chronic ductal obstruction due to inspissated intraductal secretions, which appear here as yellow-pink dense material within bile ducts.



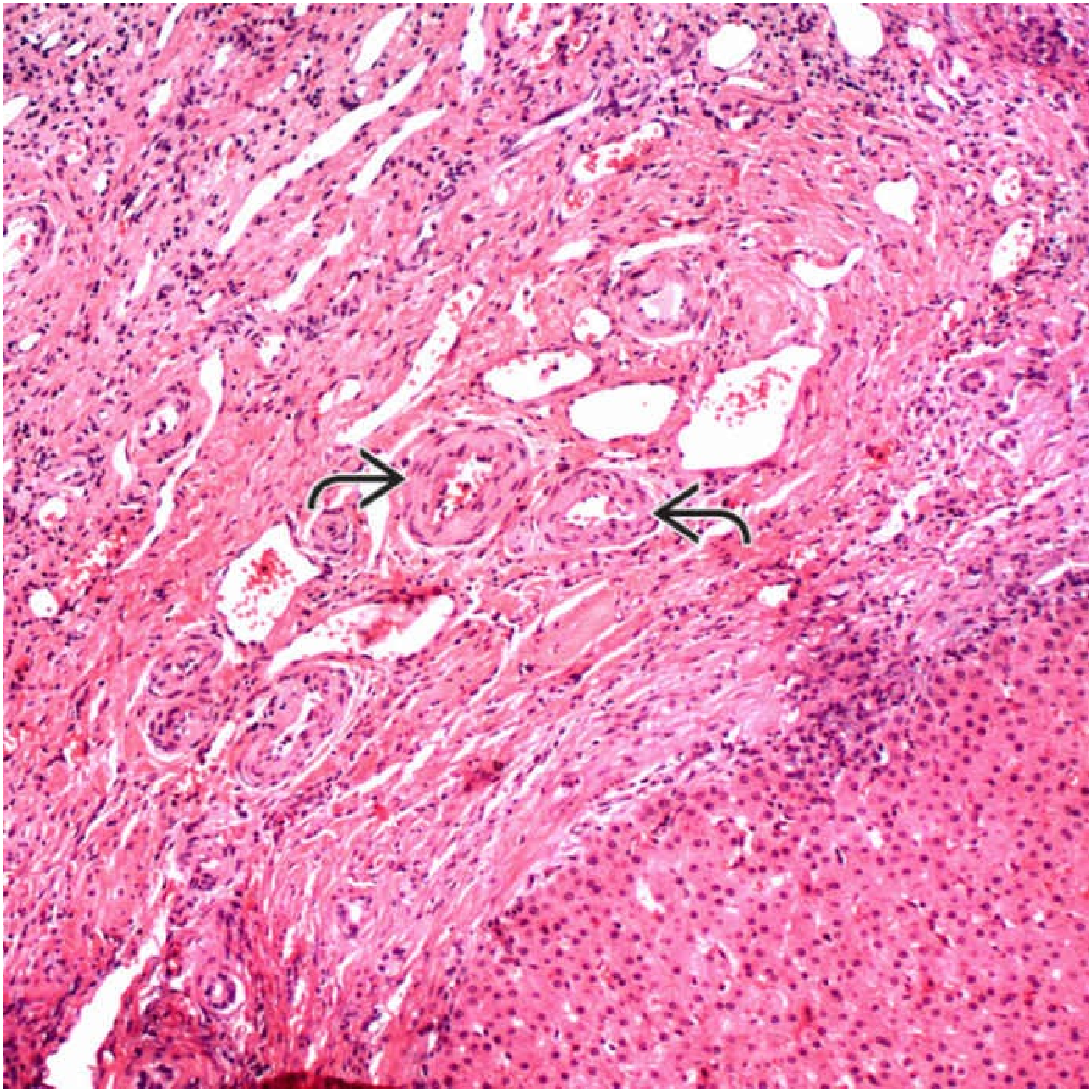
PAS-D Stain
The inspissated secretion ⇒ in cystic fibrosis is highlighted on PAS-diastase stain.



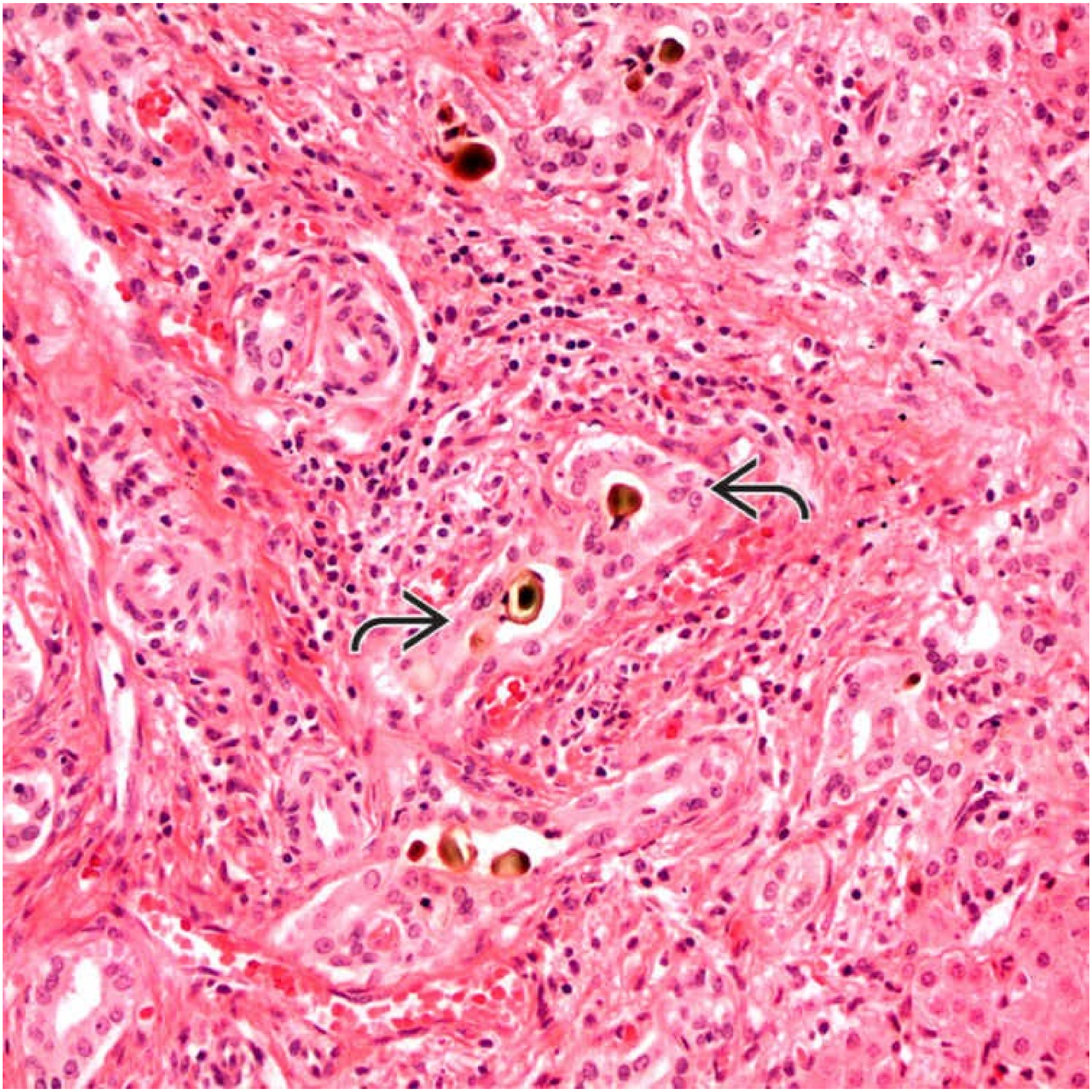
Gross Appearance
An explanted liver from a child with extrahepatic biliary atresia shows large cystic ducts filled with inspissated bile, which can mimic Caroli disease.



Large Muscular Arteries
A large portal area in an explant from a child with extrahepatic biliary atresia shows large muscular arteries ↷ and veins but no similarly sized bile ducts. At the bottom of the field are bile duct structures with inspissated bile.



Smaller Arteries
Another portal area from the same liver shows smaller arteries ↱ and veins, yet no accompanying bile ducts.



Extrahepatic Biliary Atresia
The classic picture of extrahepatic biliary atresia features bile ductular reaction with inspissated bile within the ductules ↷ .

SELECTED REFERENCES

1. Pereda, T, et al. Hereditary nonsyndromic paucity of intrahepatic bile ducts as an indication for liver transplantation. *Transplant Proc*. 2003; 35(2):719–720.
2. Yehezkely-Schildkraut, V, et al. Nonsyndromic paucity of interlobular bile ducts: report of 10 patients. *J Pediatr Gastroenterol Nutr*. 2003; 37(5):546–549.

3. Koçak, N, et al. Nonsyndromic paucity of interlobular bile ducts: clinical and laboratory findings of 10 cases. *J Pediatr Gastroenterol Nutr*. 1997; 24(1):44–48.
4. Hadchouel, M. Paucity of interlobular bile ducts. *Semin Diagn Pathol*. 1992; 9(1):24–30.

SECTION 5

DRUG/TOXIN-RELATED HEPATITIS

OUTLINE

Drug-Related Acute Hepatitis

KEY FACTS

Etiology/Pathogenesis

- 2 chief mechanisms: Intrinsic and idiosyncratic
- Herbal and botanical drugs are important but often overlooked cause of hepatotoxicity

Clinical Issues

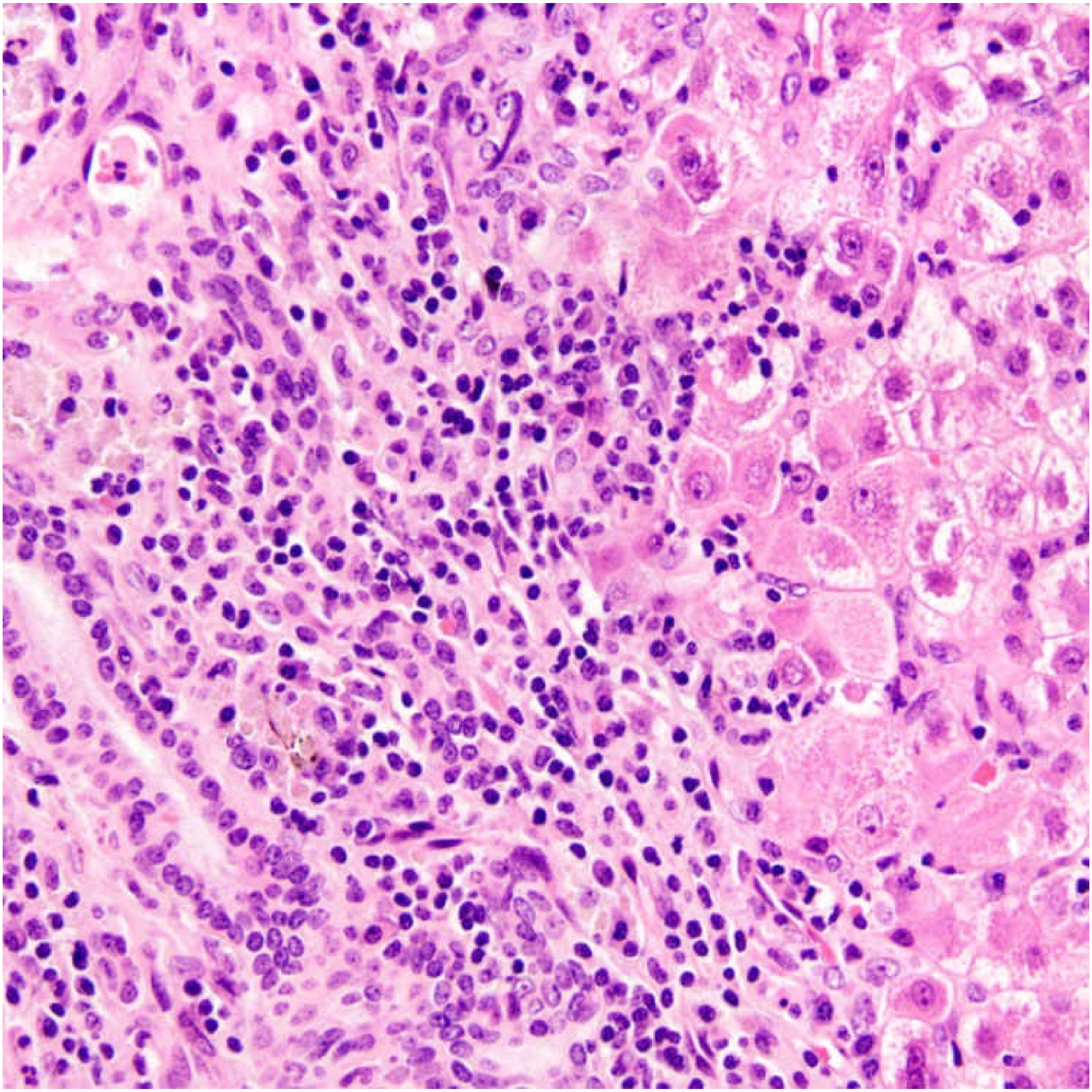
- Classified into hepatitic, cholestatic, or mixed-based pattern of enzyme elevation
  - Drug-induced liver injury (DILI) with autoimmune markers can be indistinguishable from de novo autoimmune hepatitis
  - Symptomatic and biochemical improvement in most cases on withdrawal of drug
    - Minority of cases progress to chronic hepatitis and rarely cirrhosis
    - Jaundice, high AST levels, and preexisting chronic liver disease are adverse prognostic factors

Microscopic

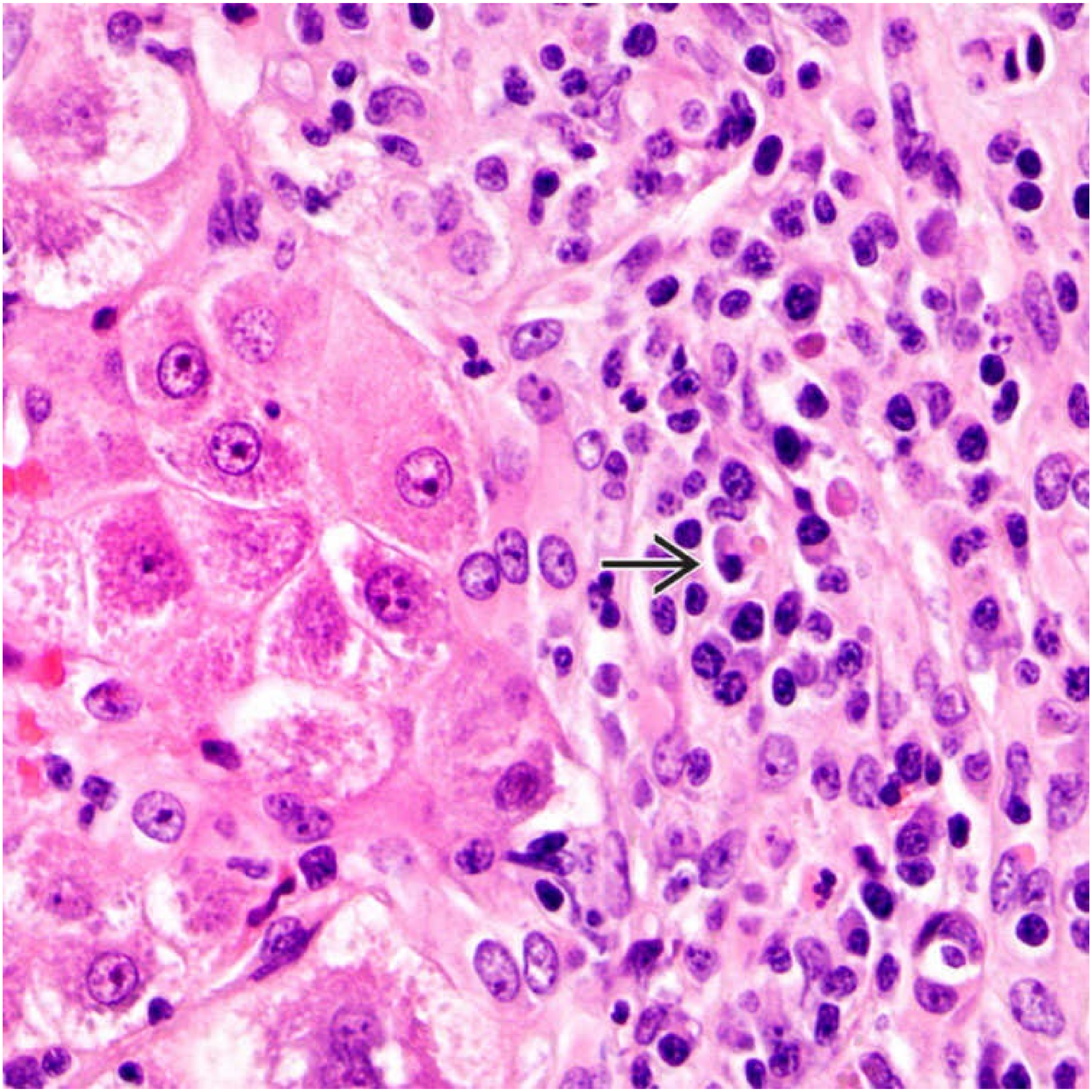
- Most medications produce inflammation-predominant pattern
- Most toxins & a few medications like acetaminophen produce necrosis-predominant pattern
- Concomitant bile duct injury, eosinophils, granulomas, perivenular necrosis, and cholestasis out of proportion to hepatocellular injury suggest DILI, but none of these are specific

Top Differential Diagnoses

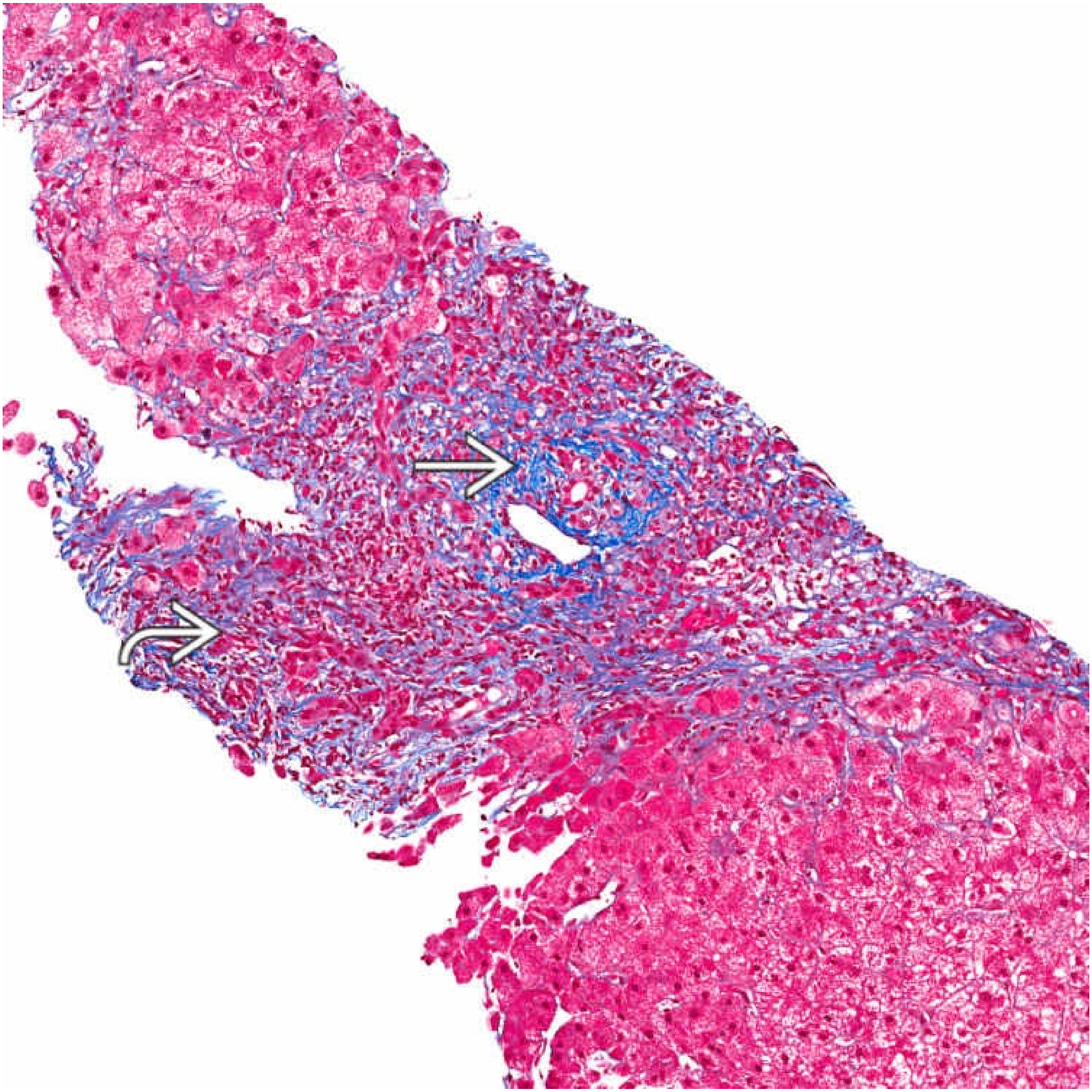
- Inflammation-predominant pattern: Acute viral hepatitis, autoimmune hepatitis, Wilson disease
- Necrosis-predominant pattern: Herpes/adenoviral hepatitis, ischemic necrosis, acute venous outflow obstruction



Portal and Interface Inflammation
The inflammation-predominant pattern of drug-related acute hepatitis features dense lymphoplasmacytic infiltrate and interface hepatocellular injury.

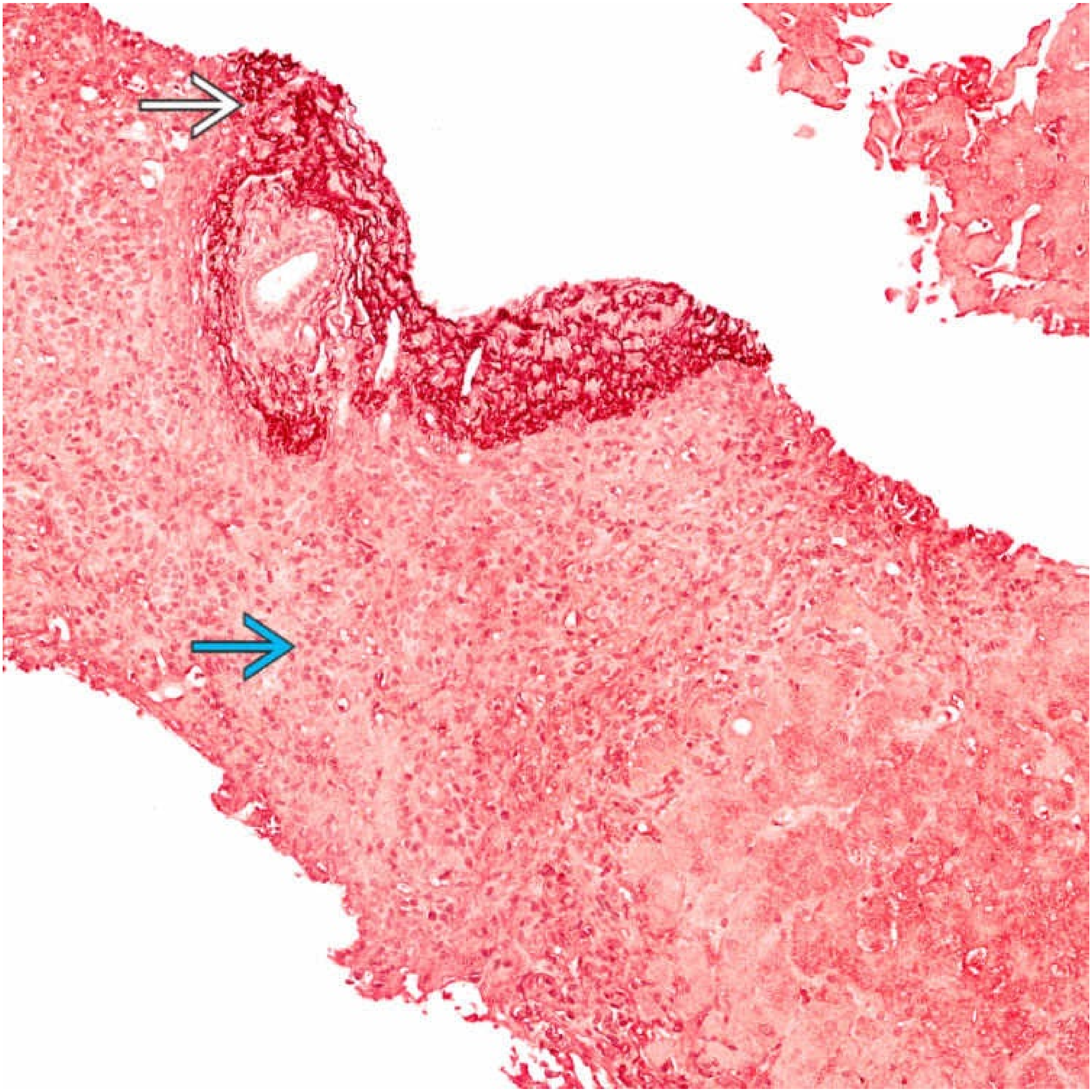


Prominent Plasma Cells
Numerous plasma cells → can be seen in drug-induced liver injury and do not necessarily indicate autoimmune hepatitis.



Trichrome Stain

The collagen in the portal tracts is coarse and stains darkly, while the periportal area with ductular reaction shows light staining. The latter indicates confluent necrosis rather than fibrosis.



Orcein Stain
The elastic fibers are highlighted in the portal tract, while the area of confluent necrosis is negative. The combination of trichrome and elastic stains help in distinguishing confluent necrosis (acute hepatitis) from fibrosis (chronic hepatitis).

TERMINOLOGY

Abbreviations

• Drug-induced liver injury (DILI)

ETIOLOGY/PATHOGENESIS

2 Chief Mechanisms

- Intrinsic hepatotoxicity
  - Predictable, dose-dependent hepatocellular damage
  - Industrial, household, or environmental toxins
  - Typically shows necrosis with negligible inflammation
- Idiosyncratic hepatotoxicity
  - Majority of adverse drug reactions fall in this category
  - Metabolic and immunological categories
    - Metabolic: Drug is metabolized into toxic metabolite in predisposed individuals
    - Immunological: Drug allergy or hypersensitivity following sensitization to drug
  - Typically shows inflammation-predominant liver injury

Herbals/Botanicals

- Important but often overlooked cause of hepatotoxicity
- Not regulated by Food and Drug Administration and hence not subject to rigorous testing
- Nearly 20% of American adults have used herbal remedies, and > 5 billion dollars are spent on these annually
- Heavy metal contaminants in these agents (arsenic, cadmium, lead, mercury) can also lead to liver toxicity

CLINICAL ISSUES

Presentation

- 3 clinical patterns
  - Hepatitic
    - Acute hepatitis with autoimmune markers may mimic autoimmune hepatitis (AIH)
    - May have features of hypersensitivity like rash, arthralgia, and peripheral eosinophilia
    - Progression to chronic hepatitis with fibrosis and even cirrhosis can occur
  - Cholestatic
  - Mixed
- Classified into acute or chronic based on duration of injury
- Establishing drug as causative agent is key
  - Temporal profile of onset of liver dysfunction is crucial
  - Liver toxicity may manifest weeks or months after drug ingestion and even after drug has been stopped
  - Systematic literature search is necessary
  - If observed pattern has been reported, case for DILI is strengthened
  - Rechallenge can confirm drug etiology but is rarely done

Laboratory Tests

- Measurement of serum levels of drug or its metabolite can be helpful in diagnosis (e.g., acetaminophen toxicity)
- Antinuclear &/or antismooth muscle antibodies
- Transaminase elevations may be marked

Treatment

- Drug withdrawal
- Steroids may be necessary

Prognosis

- Improvement in most cases on drug withdrawal
- Liver enzymes can remain elevated for up to several months after discontinuation of drug
- Minority of cases progress to chronic hepatitis, and rarely, cirrhosis (despite drug withdrawal)
- Jaundice, high AST levels, and preexisting chronic liver disease are adverse prognostic factors

MICROSCOPIC

Histologic Features

- Acute hepatitis: Inflammation-predominant pattern
  - Portal and parenchymal inflammation with hepatocellular injury
  - Necrosis can affect single hepatocyte (spotty necrosis) or groups of hepatocytes (confluent necrosis)
  - By definition, fibrosis is absent
  - Regenerative features like binucleate hepatocytes and thick cell plates
  - Prominent Kupffer cells often are present in sinusoids
- Acute hepatitis: Necrosis-predominant pattern
  - Necrosis with minimal inflammation
  - Periportal (zone 1): Cocaine, ferrous sulphate
  - Midzonal (zone 2): Beryllium
  - Centrizonal (zone 3): Acetaminophen, halothane, carbon tetrachloride
  - Acute hepatic failure with extensive necrosis
- Resolving hepatitis pattern
  - Minimal-mild hepatocellular injury & inflammation
  - Numerous macrophages highlighted by PAS-D stain
- Syncytial giant cell hepatitis pattern
  - Uncommon pattern of hepatic DILI
  - Severity can range from mild to fulminant

Predominant Pattern/Injury Type

- Inflammatory

Predominant Cell/Compartment Type

• Hepatocyte

DIFFERENTIAL DIAGNOSIS

Acute Hepatitis: Inflammation-Predominant Pattern

• Acute viral hepatitis, AIH, Wilson disease
• Clinical and serological information necessary for final diagnosis
• Concomitant bile duct injury, eosinophils, granulomas, perivenular necrosis, cholestasis out of proportion to hepatocellular injury suggest DILI, but are not specific
• Autoantibodies, elevated IgG, prominent plasma cells favor AIH

Acute Hepatitis: Necrosis-Predominant Pattern

• Herpes and adenoviral hepatitis, ischemic necrosis, acute venous outflow obstruction
• Viral inclusions in herpes and adenoviral hepatitis
• Clinical information necessary to distinguish DILI from necrosis due to vascular etiologies

Resolving Hepatitis Pattern

• Nonspecific reactive hepatitis in systemic diseases
• Viral hepatitis

Syncytial Hepatitis Pattern

• AIH, paramyxovirus, hepatitis C, human immunodeficiency virus hepatitis
• Distinction based on clinical and serological features

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

• Elevated liver enzymes in variety of patterns temporally associated with drug

Pathologic Interpretation Pearls

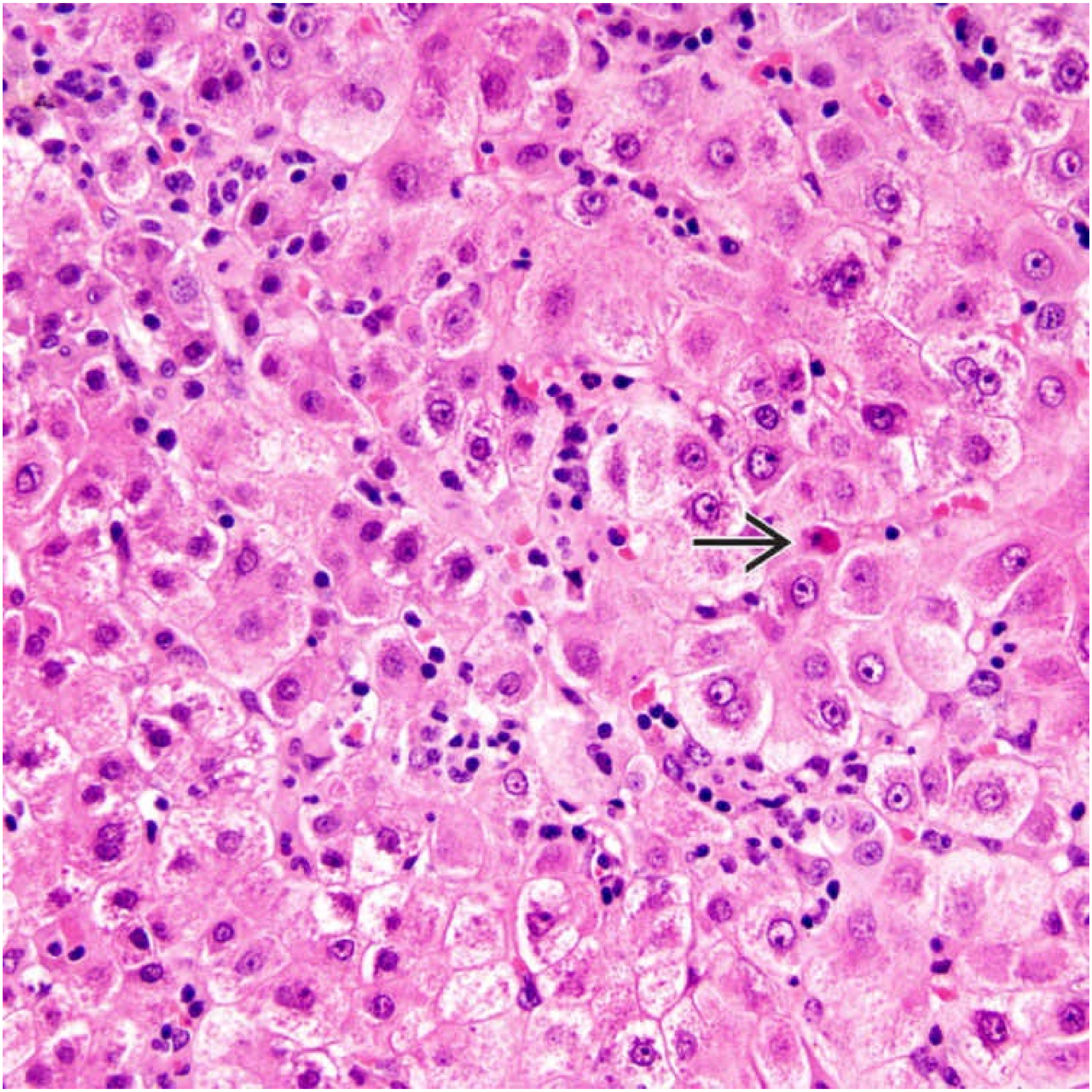
• Multiple patterns of enzyme elevation and liver injury
• Medication history, including herbal/botanical drugs

CIOMS Consensus Criteria for Terminology in Drug-Induced Liver Injury

Terminology	Criteria
Hepatocellular injury	Isolated increase in ALT > 2x normal, or ALT/ALP ratio > 5
Cholestatic injury	Isolated increase in ALP > 2x normal, or ALT/ALP ratio < 2
Mixed injury	Both ALT and ALP are increased; ALT/ALP ratio between 2 and 5
Acute injury	Above changes present for < 3 months
Chronic injury	Above changes present for > 3 months
Chronic liver disease	This term is used only after histologic confirmation

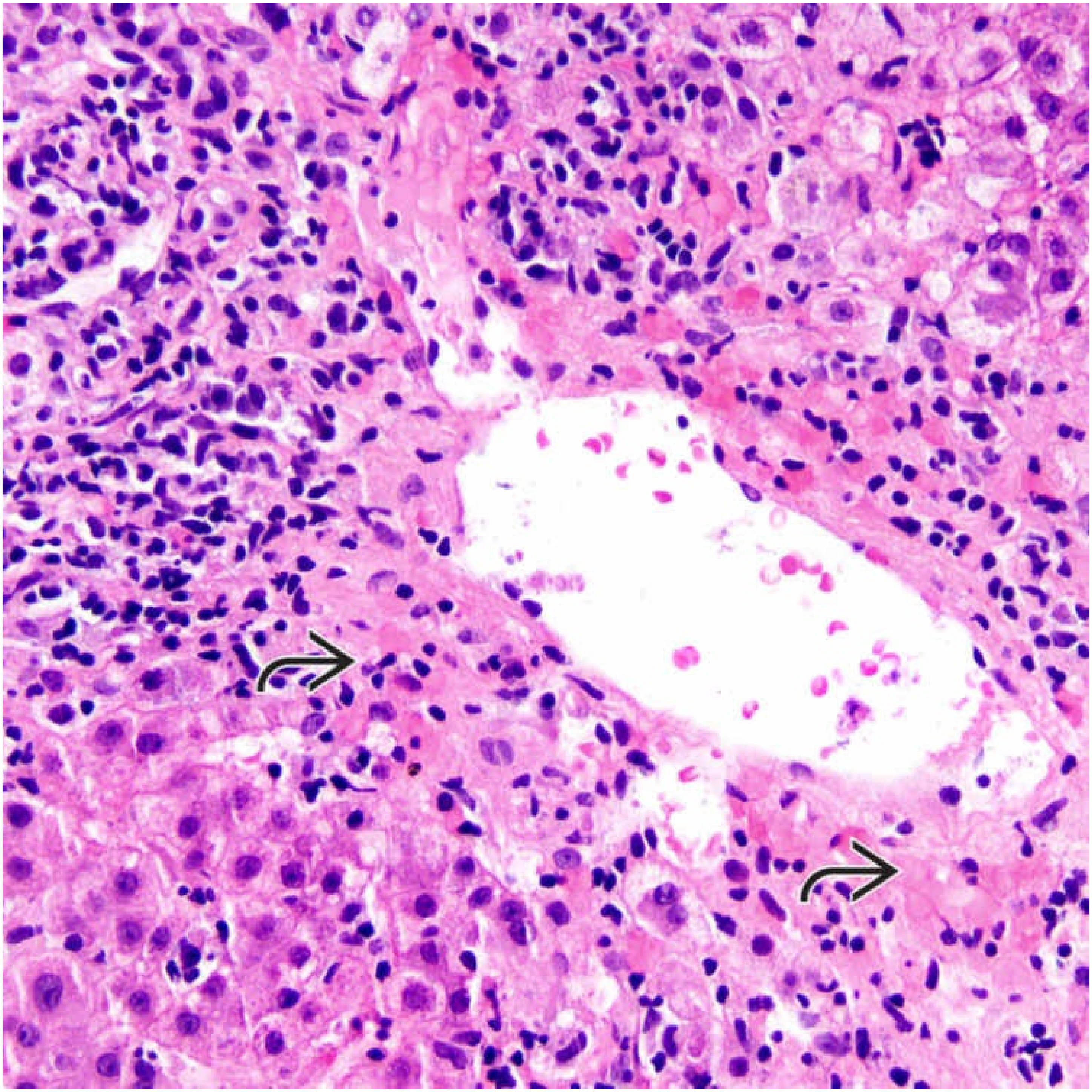
Drugs Associated With Acute Hepatitis Pattern of Injury

Class of Drugs	Individual Drugs
Inflammation-Predominant Pattern	
Nonsteroidal antiinflammatory drugs	Indomethacin, tolmetin, sulindac, ibuprofen, ketoprofen, mefenamic acid, celecoxib
Anticonvulsants	Phenytoin, valproic acid
Antibacterial agents	Ampicillin, amoxicillin-clavulanic acid, oxacillin, cephalosporins, tetracycline, sulfonamides, erythromycin, trimethoprim-sulfamethoxazole
Antifungal	Griseofulvin, fluconazole, ketoconazole
Antiparasitic	Albendazole, thiabendazole, sulfadoxine/pyrimethamine
Antituberculous	Isoniazid, rifampin
Antiviral	Zidovudine, ribavirin
Antitumor	6-mercaptopurine, azathioprine, L-asparaginase, mithramycin, vincristine, cyclophosphamide, carmustine
Antihypertensive	Methyldopa, hydralazine, lisinopril, labetalol
Antiarrhythmic	Quinidine, procainamide
Hypolipidemics	Statins, clofibrate, nicotinic acid
Hypoglycemics	Rosiglitazone, troglitazone
Others	Sulfonylureas, troglitazone, dantrolene, chlorzoxazone, dextropropoxyphene, allopurinol, gold
Herbal agents	Chapparal leaf, mistletoe, germander, kava, lycopodium
Necrosis-Predominant Pattern	
Drugs and toxins	Drugs: Acetaminophen, halothane; toxins: Aflatoxin, death cap mushroom (*Amanita phalloides*), carbon tetrachloride, ethylene dichloride, allyl compounds, ferrous sulfate phosphorus, MDMA (ecstasy)
Herbal agents	Pennyroyal, glue thistle, germander
AIH type 1-like disease	Minocycline, nitrofurantoin, alpha-methyl dopa
AIH type 2-like disease	Hydralazine
Drugs	Methotrexate, p-aminosalicylic acid, 6-mercaptopurine, clomethacin, ticlopidine
Herbal agents	Isabgol

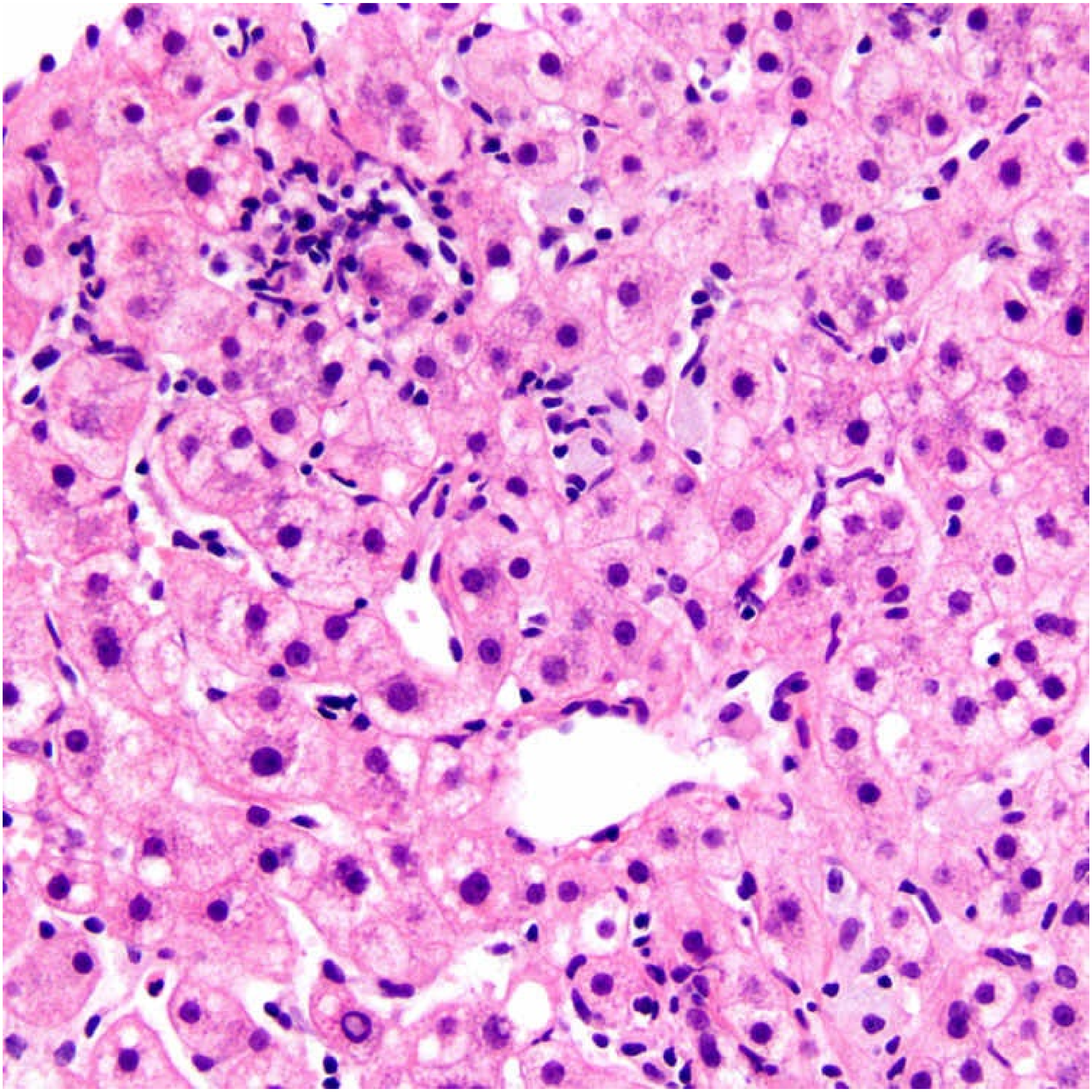


Parenchymal Injury

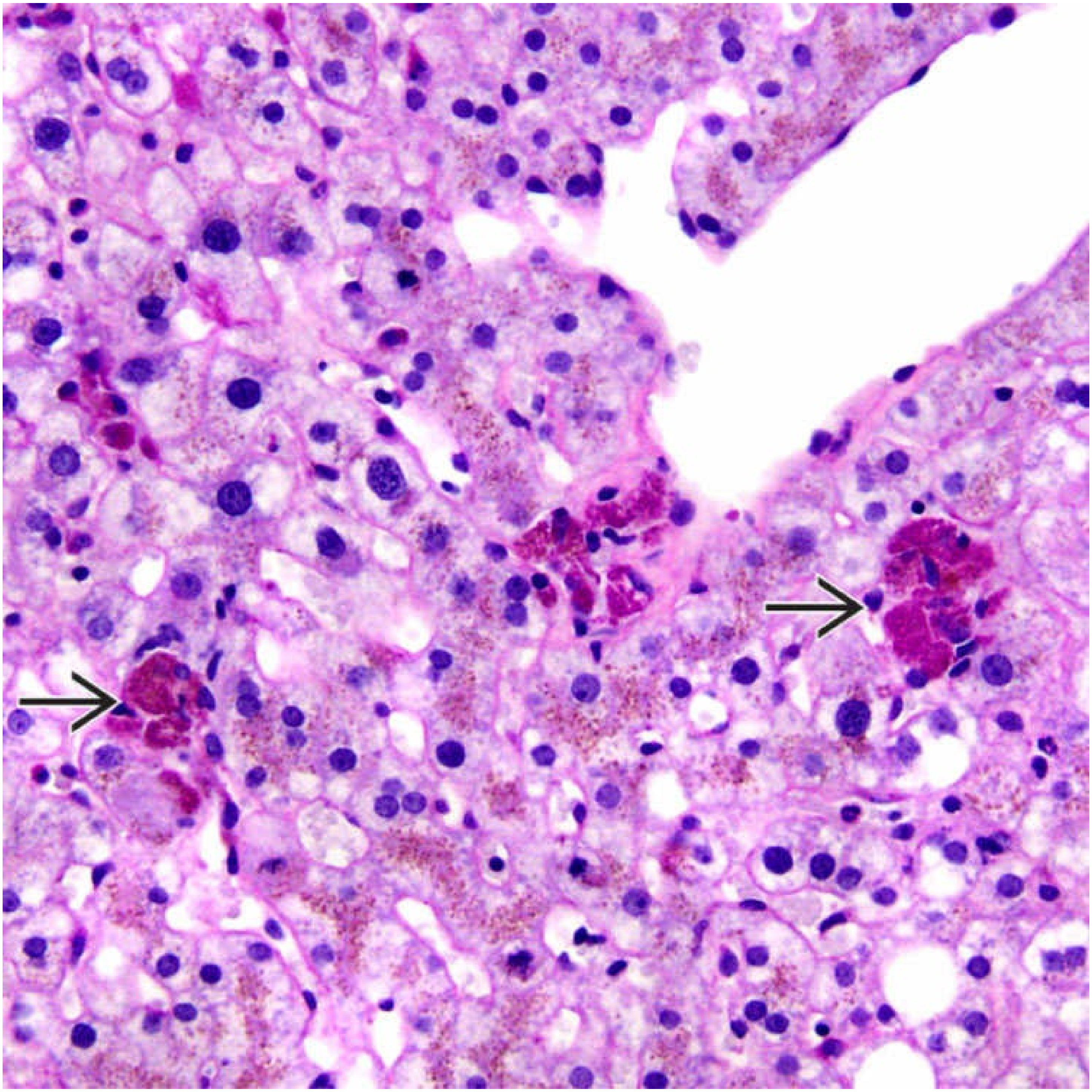
Lobular hepatitis in a case of drug-induced hepatitis features mild inflammation, swollen hepatocytes, and occasional hepatocyte dropout →. The features are indistinguishable from other etiologies of acute hepatitis.



Necrosis Around Central Vein
Centrizonal necrosis with lymphoplasmacytic inflammation is not a specific finding but is highly suggestive of drug-induced liver injury.

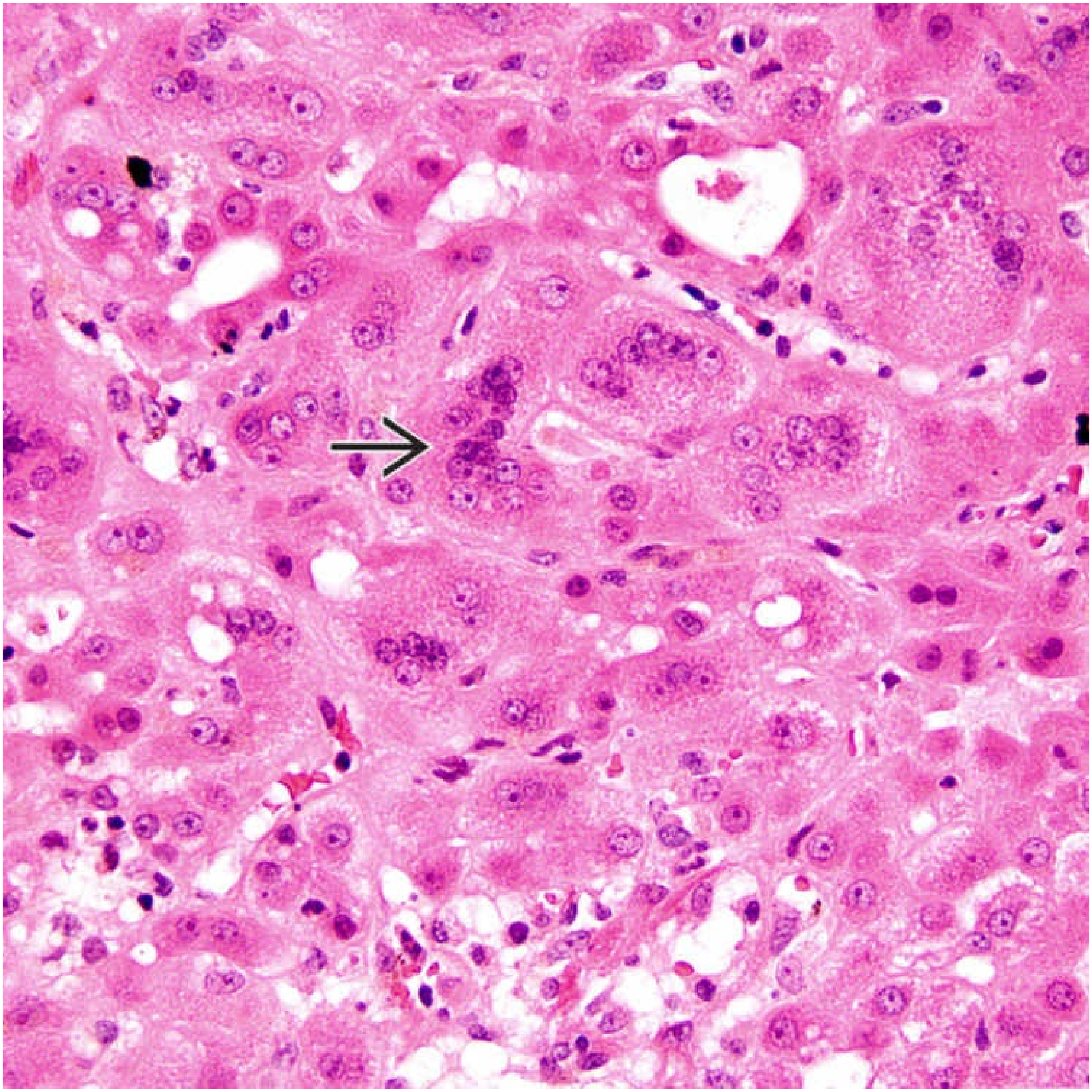


Mild Lobular Inflammation
Resolving drug-induced hepatitis shows mild lobular inflammation, minimal hepatocellular injury, and scattered macrophages along the sinusoids.

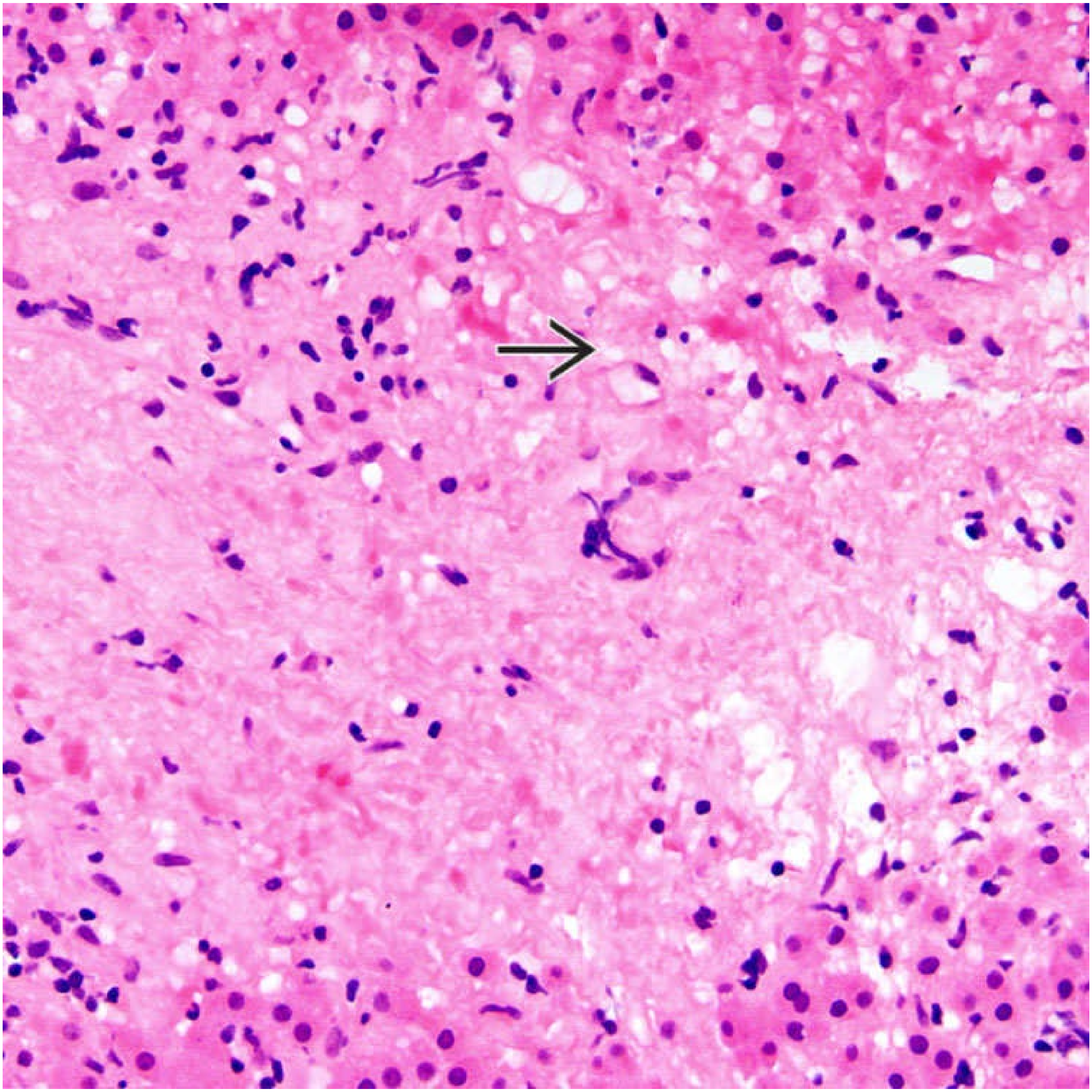


PAS-Diastase Stain

Macrophages in the sinusoids → in resolving drug-induced hepatitis are highlighted by PAS-D stain.



Multinucleated Hepatocytes
Syncytial giant cell hepatitis, characterized by numerous multinucleated hepatocytes →, is a rare pattern of acute drug-induced liver injury.



Necrosis Without Inflammation
Necrosis-predominant drug-induced liver injury → with minimal inflammation is difficult to histologically distinguish from ischemic injury.

SELECTED REFERENCES

1.Kleiner, DE, et al. Hepatic histological findings in suspected drug-induced liver injury: systematic evaluation and clinical associations. *Hepatology*. 2014; 59(2):661–670.

2.Suzuki, A, et al. The use of liver biopsy evaluation in discrimination of idiopathic autoimmune hepatitis versus drug-induced liver injury. *Hepatology*. 2011; 54(3):931–939.

3.Andrade, RJ, et al. Outcome of acute idiosyncratic drug-induced liver injury: Long-term follow-up in a hepatotoxicity registry. *Hepatology*. 2006; 44(6):1581–1588.

4.Watkins, PB, et al. Drug-induced liver injury: summary of a single topic clinical research

conference. *Hepatology*. 2006; 43(3):618–631.
5. Andrade, RJ, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. *Gastroenterology*. 2005 Aug; 129(2):512–521. [Erratum in: Gastroenterology. 129(5): 1808, 2005].
6. Björnsson, E, et al. Outcome and prognostic markers in severe drug-induced liver disease. *Hepatology*. 2005; 42(2):481–489.

Drug-Induced Acute Hepatic Failure

KEY FACTS

Terminology

- Onset of hepatic encephalopathy within 8 weeks of onset of symptoms
    - INR is > 1.5, and there is no evidence of chronic liver disease
- Corresponding pathologic terms: Massive/submassive necrosis, fulminant hepatitis

Clinical Issues

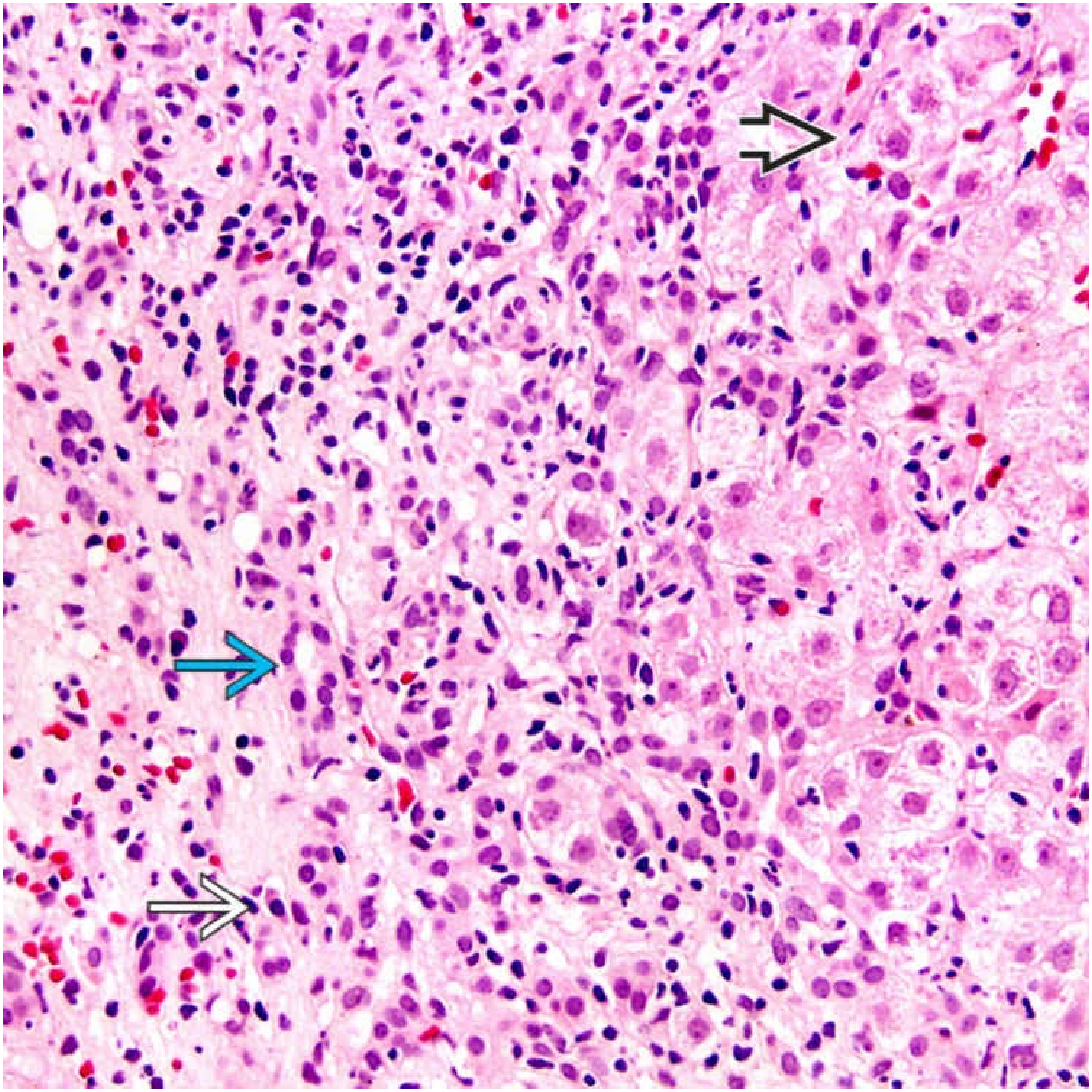
- Acetaminophen is most common cause of acute liver failure (ALF) in USA, accounting for 40-50% of cases

Microscopic

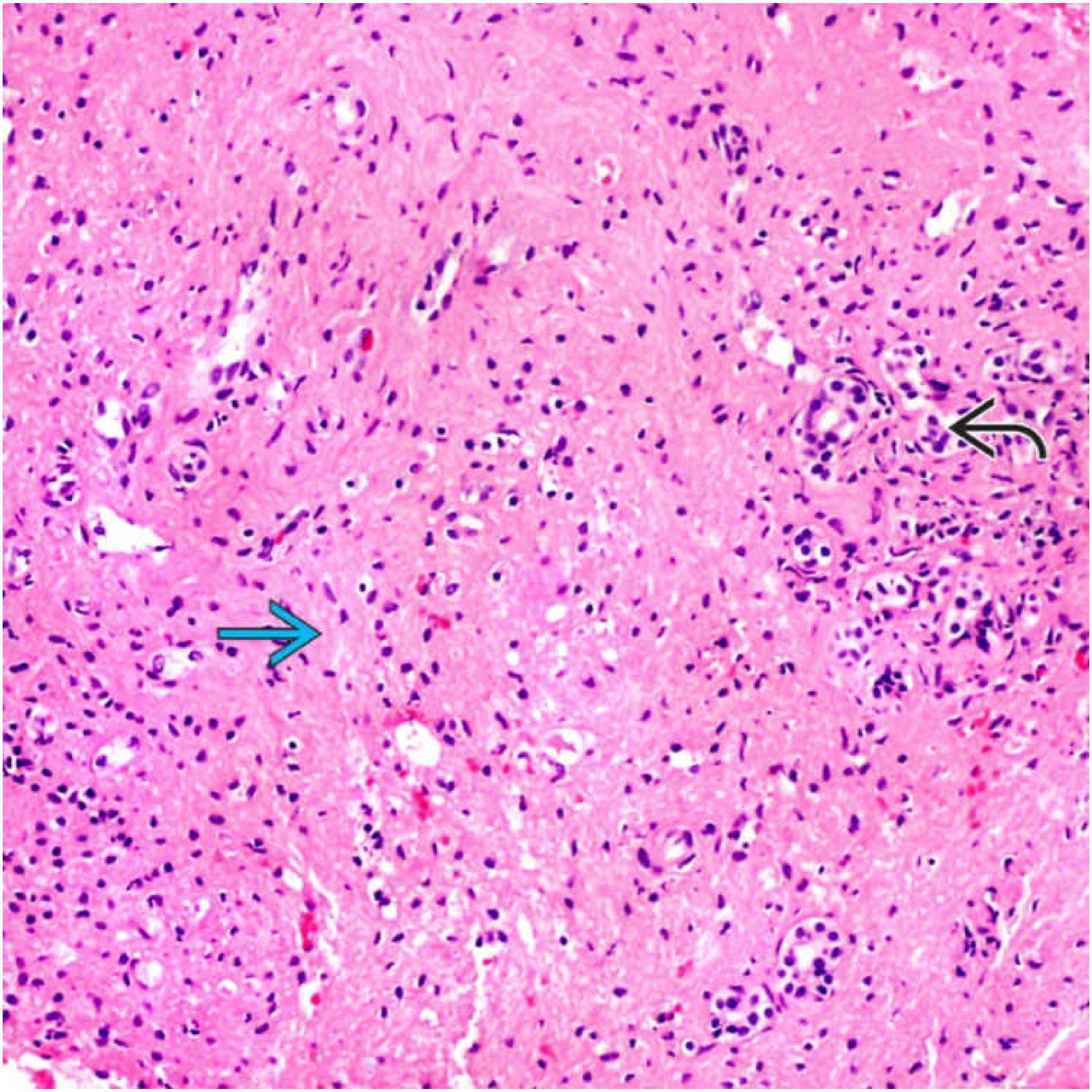
- Massive/submassive necrosis with little or no inflammation: Acetaminophen, most toxins
- Massive/submassive necrosis with prominent inflammation: Most idiosyncratic drug reactions
- Microvesicular steatosis: Tetracycline, zidovudine
- Regenerative nodules can be seen later in course of disease and can be mistaken for cirrhosis
- Unlike fibrous septa of cirrhosis, necrotic areas show pale staining with trichrome stain and lack elastic fibers on elastic stain

Top Differential Diagnoses

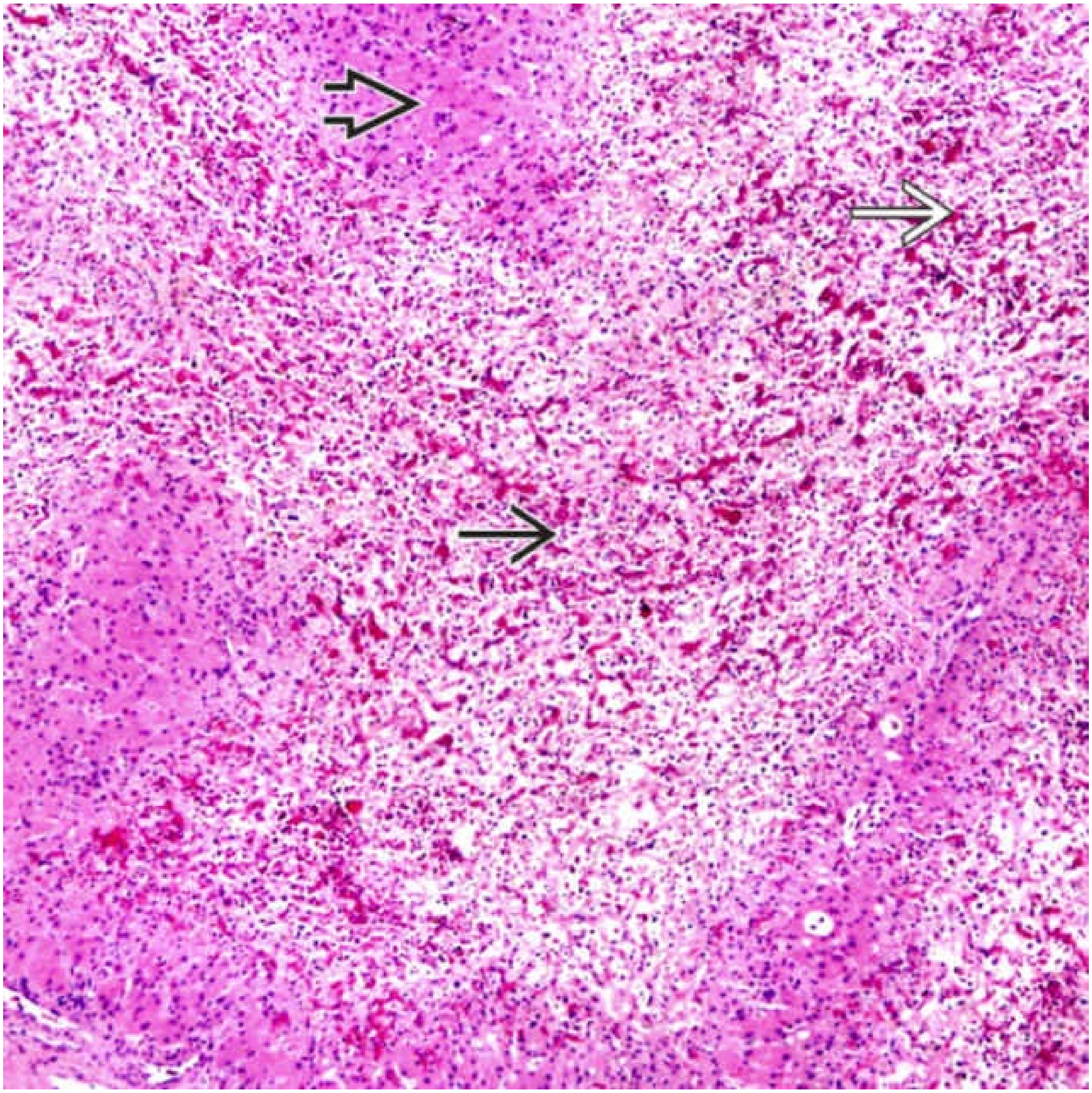
- Necrosis with inflammation: Acute viral hepatitis A and B, autoimmune hepatitis, Wilson disease
- Necrosis with minimal inflammation: Herpes simplex and adenoviral hepatitis, acute ischemia, acute Budd-Chiari syndrome
- Microvesicular steatosis: Alcoholic foamy degeneration, acute fatty liver of pregnancy, Reye syndrome, Jamaican vomiting sickness, rare metabolic disorders like carnitine deficiency



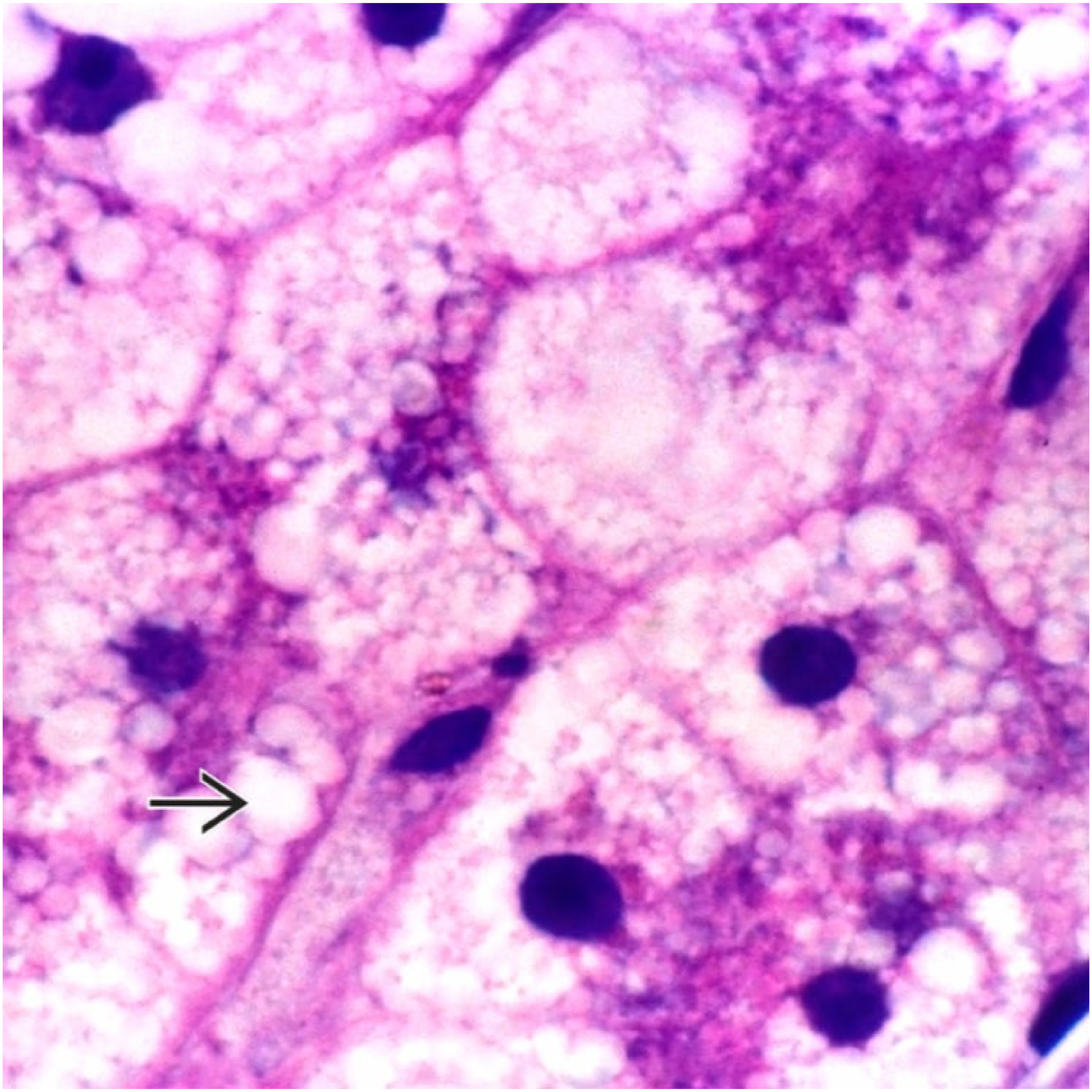
Necrosis and Inflammation
This image shows confluent necrosis with lymphoplasmacytic inflammation. Swelling, inflammation, and regenerative changes are seen in the remaining parenchyma. Ductular reaction is a common finding in the setting of necrosis and does not necessarily signify biliary disease.



Necrosis Without Inflammation
This image shows extensive panacinar necrosis with negligible inflammation, findings typical of toxic pattern of drug injury.



Acetaminophen-Related Acute Liver Failure
Multiacinar hemorrhagic necrosis →, congestion ⇒, and lack of inflammation with sparing of periportal hepatocytes ➪ are typical of acetaminophen toxicity but can also be seen in acute ischemia and acute Budd-Chiari syndrome.



Microvesicular Steatosis
Multiple small fat droplets are seen filling the cytoplasm →. There is no necrosis or inflammation.

TERMINOLOGY

Abbreviations

- Acute liver failure (ALF)

Definitions

- Hepatic encephalopathy and reduced synthetic function evidenced by INR > 1.5
  - Duration of disease less than 26 weeks

- Absence of chronic liver disease
  - Corresponding pathologic term is massive/submassive necrosis or fulminant hepatitis

ETIOLOGY/PATHOGENESIS

Mechanisms of Injury

- Massive/submassive necrosis due to intrinsic hepatotoxins
  - Most toxins fall in this category
  - – Carbon tetrachloride, mushroom poisoning, recreational drugs like cocaine and MDMA (ecstasy)
  - Very few drugs cause this pattern of injury
    - – Acetaminophen, halothane
    - – Herbal medications: Pennyroyal, glue thistle, germander
- Massive/submassive necrosis due to idiosyncratic injury
  - Most drugs fall in this category
    - – Drugs used for treatment of tuberculosis such as isoniazid are one of leading culprits of ALF in developing world
    - – Other implicated drugs: Monoamine oxidase inhibitors, anticonvulsants (valproate, phenytoin), antimicrobial agents (sulfonamides, co-trimoxazole, ketoconazole)
- Diffuse microvesicular steatosis due to acute mitochondrial injury
  - Presents as ALF without histological necrosis
  - Commonly implicated drugs: Tetracycline, zidovudine, valproic acid, amineptine

CLINICAL ISSUES

Presentation

- Depends on specific drug or toxin
  - Acetaminophen is most common cause of ALF in USA accounting for 40-50% of cases
  - Dose-dependent toxicity occurs with accidental (1/3 of cases) or suicidal (2/3 of cases) overdose
  - Minimum toxic dose in adults is 7.5-10 g, but severe liver damage occurs with ingestion of 15-25 g
  - Chronic alcohol consumption, obesity, and drugs that induce P-450 cytochrome system can lower toxic threshold of acetaminophen
  - Gastrointestinal symptoms for 1st 12-24 hours and latent phase of 24-48 hours is followed by ALF 72-96 hours after drug ingestion

Treatment

- Drug withdrawal, supportive care, and liver resuscitation (hypothermia, albumin dialysis, artificial liver support)
- Liver transplantation is often necessary
- Acetaminophen hepatotoxicity can be prevented with acetylcysteine therapy within 12 hours of drug ingestion

Prognosis

- Severe encephalopathy and older age are adverse prognostic factors for spontaneous recovery
- For acetaminophen toxicity, blood levels 4-16 hours after ingestion are best predictor of outcome; highest mortality is encountered in late presenters

MICROSCOPIC

Histologic Features

- 4 histologic patterns of injury
  - Massive/submassive necrosis with little or no inflammation
  - Extensive confluent hepatocellular necrosis
  - Necrosis may be nonzonal, centrizonal (acetaminophen, halothane, carbon tetrachloride), midzonal (beryllium), or periportal (cocaine, ferrous sulphate)
  - Concomitant steatosis, often microvesicular, can be present (carbon tetrachloride poisoning, cocaine)
  - Mild or absent inflammation
- Massive/submassive necrosis with prominent inflammation
  - Portal and panacinar lymphocytic inflammation, variable eosinophils and plasma cells
  - Confluent necrosis common
- Extensive microvesicular steatosis
  - Hepatocyte cytoplasm diffusely filled with small fat droplets
  - Inconspicuous inflammation and necrosis
- Massive/submassive necrosis with regenerative nodules
  - Regenerative nodules can be seen later in course of disease and mistaken for cirrhosis
  - Area between nodules is not fibrous septa of cirrhosis but bridging necrosis with collapse of liver parenchyma
  - Trichrome stain: Pale staining in necrotic areas unlike coarse, dense staining in fibrous septa of cirrhosis
  - Elastic stain: Lack of elastic fibers in necrotic areas unlike fibrous septa of cirrhosis, which are richly endowed with elastic fibers
    - Trichrome stain is more reliable than elastic stain to distinguish necrosis and fibrosis

DIFFERENTIAL DIAGNOSIS

Acute Viral Hepatitis

- Hepatotropic viruses
  - In USA and Europe, only accounts for 10-15% of cases (5-10% each by hepatitis A and B)
  - Hepatitis C has been reported to cause ALF in Asia but rarely in Western world
  - Coinfection or superinfection with hepatitis D can lead to ALF
  - Hepatitis E has been associated with ALF in Indian subcontinent, especially in pregnant women
- Nonhepatotropic viruses
  - Herpes simplex and adenovirus infection can lead to ALF with necrosis-predominant pattern of injury

- Less common infections: CMV, Epstein-Barr virus, yellow fever, dengue fever, Ebola fever
- Parvovirus B19 can cause fulminant hepatitis in children

Autoimmune Hepatitis

- Rapid deterioration of liver function can lead to ALF
- Extensive necroinflammatory activity with plasma cell-rich infiltrate
- Histologically indistinguishable from idiosyncratic drug reaction
- Autoantibodies, elevated serum IgG, and presence of fibrosis on biopsy favor autoimmune hepatitis

Histological Patterns of Injury in Acute Liver Failure

Histological Pattern	Drugs Implicated	Differential Diagnosis
Massive/submassive necrosis with minimal inflammation	Acetaminophen, cocaine, MDMA (ecstasy), carbon tetrachloride	Herpes simplex or adenoviral hepatitis, acute ischemic injury, acute Budd-Chiari syndrome, Wilson disease
Massive/submassive necrosis with prominent inflammation	Isoniazid, monoamine oxidase inhibitors, anticonvulsants (phenytoin, valproate), antimicrobials (sulfonamides, cotrimoxazole, ketoconazole)	Autoimmune hepatitis, viral hepatitis, Wilson disease
Microvesicular steatosis	Tetracycline (antibiotic), zidovudine (nucleoside analogue), valproic acid (anticonvulsant), amineptine (antidepressant)	Acute alcohol intoxication, Reye syndrome, acute fatty liver of pregnancy

Ischemic Liver Injury

- Causes
  - Cardiogenic or septic shock
  - Variceal hemorrhage
- Inflammation is typically mild or absent, mimicking toxic pattern of drug-induced injury
- Histologic features favoring ischemia
  - Centrizonal or panacinar necrosis with congestion and pooling of blood in zone 3 sinusoids
  - Periportal cholangiolar bile plugs in cholangioles (cholangitis lenta) in absence of demonstrable biliary obstruction

Acute Budd-Chiari Syndrome

- Acute presentation is rare, can mimic ischemia or toxic pattern of drug injury
- Centrizonal or panacinar necrosis with hemorrhage, congestion, and sinusoidal dilatation

Wilson Disease

- Rare but important cause of ALF in young patients (presentation after 50 years is rare)
  - Recovery of hepatic function is rare in fulminant Wilson disease, and transplantation is only viable option
- Can mimic toxic as well as idiosyncratic drug reaction
  - Hemolytic anemia, if present, favors Wilson disease
  - AST:ALT > 2.2, high bilirubin (> 20 mg/dL), and low alkaline phosphatase has high specificity for Wilson disease
  - Serum ceruloplasmin, urinary copper, or quantitative determination of hepatic copper from paraffin block helps in establishing diagnosis

Malignant Neoplasms

- Infiltration of liver by malignant neoplasms rarely leads to ALF
  - Implicated tumors include leukemia/lymphoma, metastatic carcinoma, and melanoma
- Identification of tumor as underlying etiology is important to avoid transplantation as prognosis is poor

Pregnancy-Related Acute Liver Failure

- HELLP syndrome
  - Hemolysis (H), elevated liver (EL) enzymes, and low platelets (LP)
  - Serious complication of preeclampsia, occurs in 3rd trimester
  - ALF is rare complication
  - Histologically shows focal necrosis, periportal hemorrhage, and fibrin deposits
- Acute fatty liver of pregnancy
  - Occurs in 3rd trimester, often associated with preeclampsia
  - Hyperbilirubinemia and elevations of ALT and AST are modest compared to other causes of ALF
  - Increase in blood pressure, hyperuricemia, and intense thirst favor this diagnosis
  - Liver biopsy is often not done due to risk of bleeding
  - Histologically shows microvesicular steatosis, hepatocellular swelling, inconspicuous necrosis

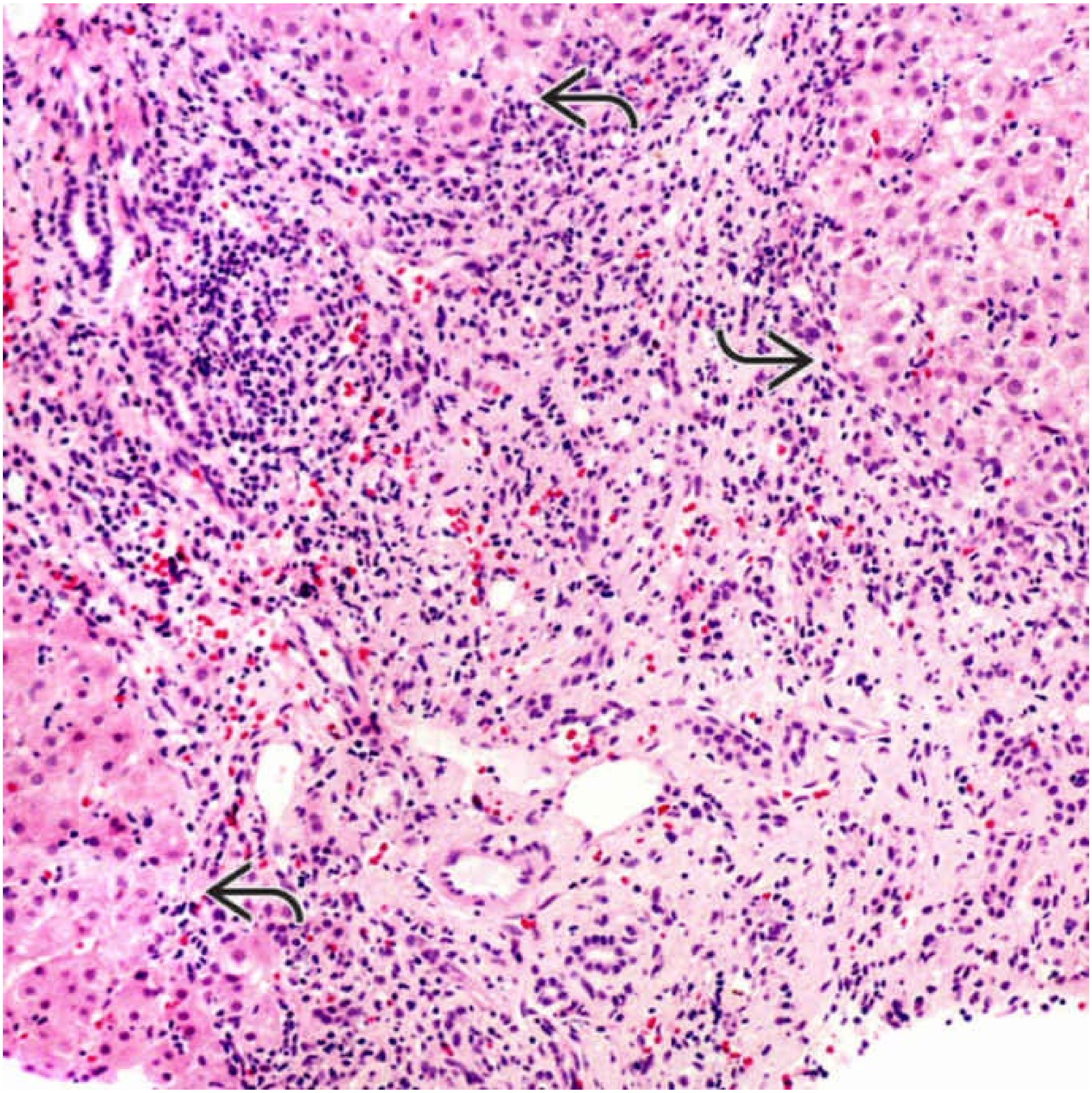
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

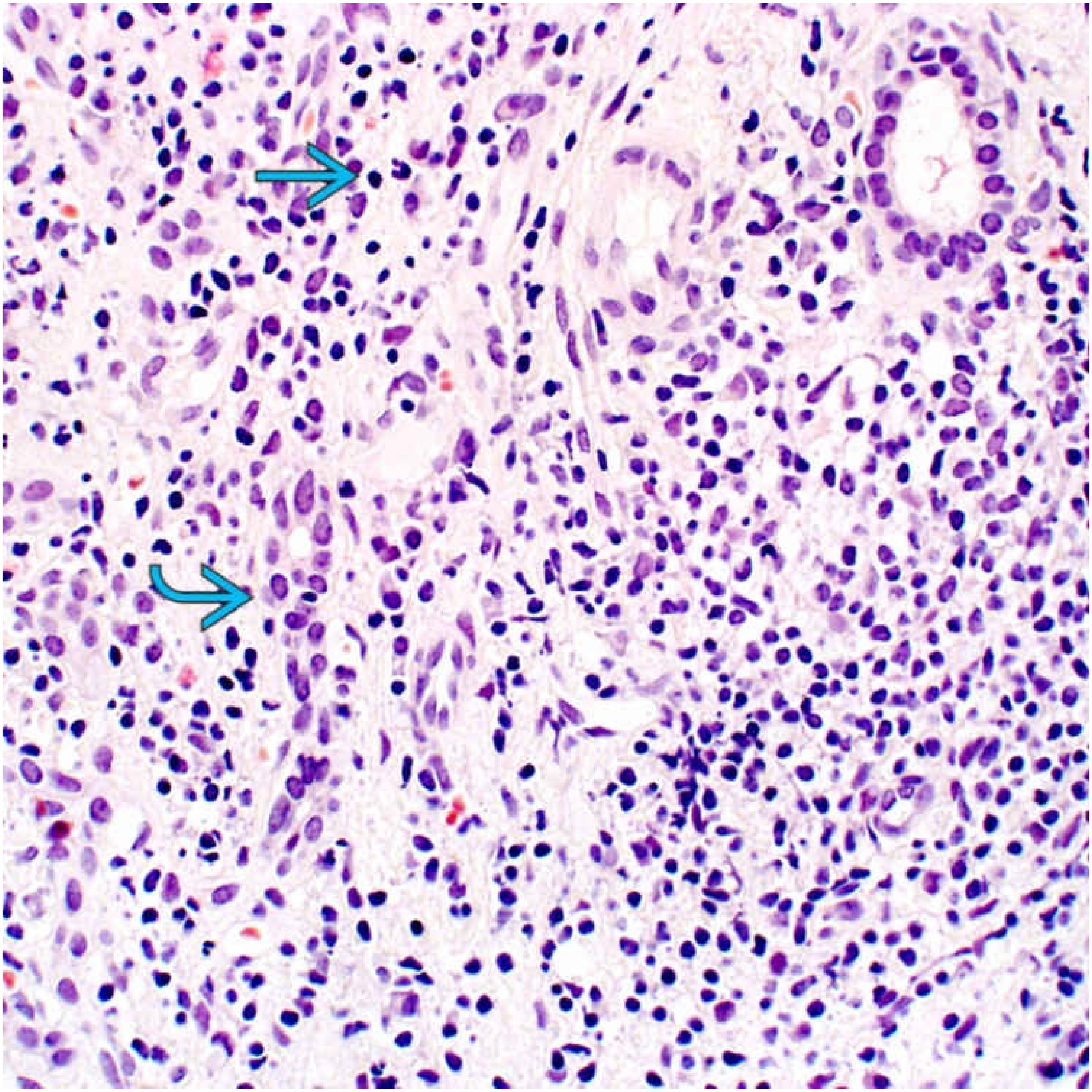
- ALF in patient who has been exposed to drug or toxin

Pathologic Interpretation Pearls

- Necrosis that may be significantly out of proportion to inflammation

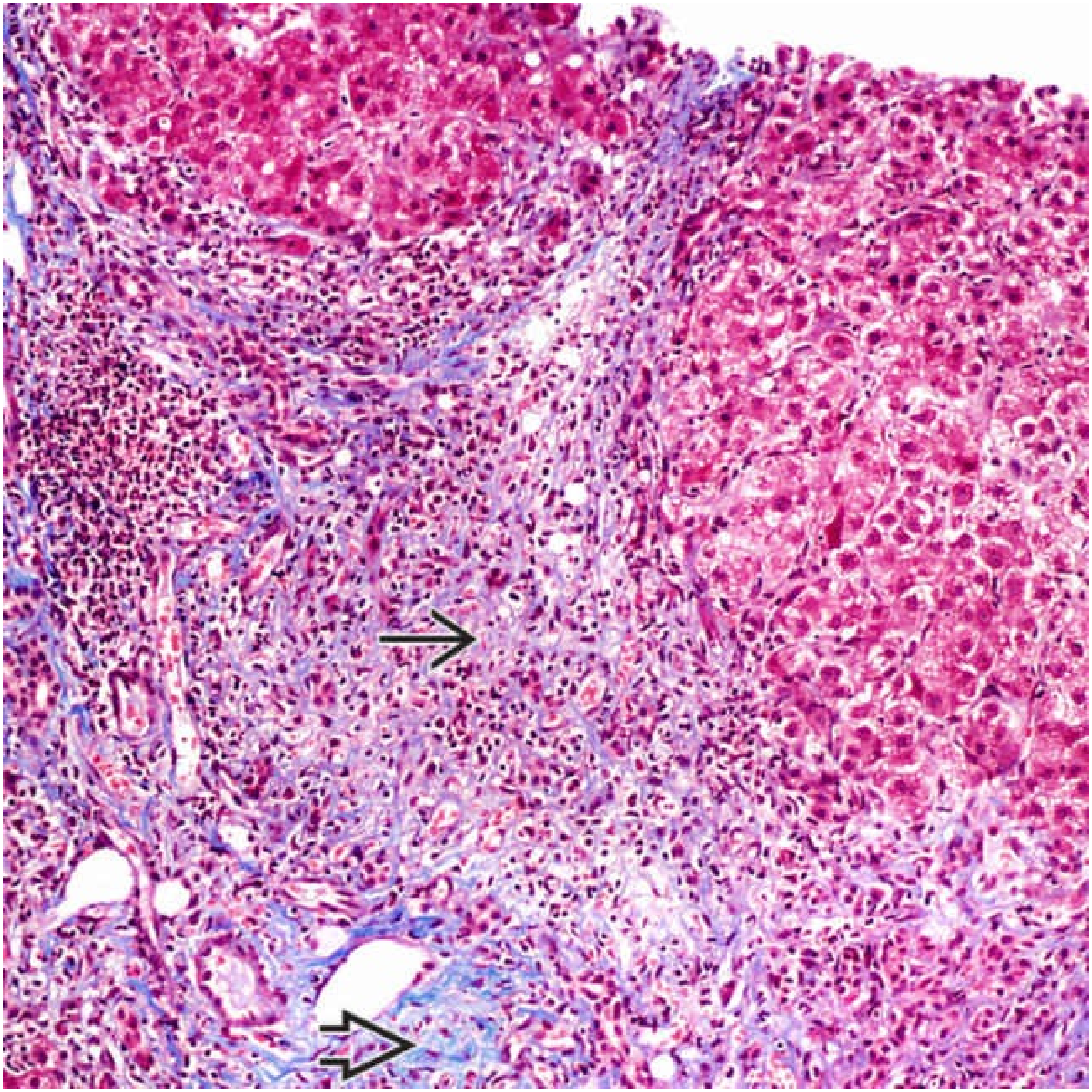


Regenerative Nodules
Regenerative nodules of liver parenchyma are separated by areas of bridging necrosis, mimicking cirrhosis.



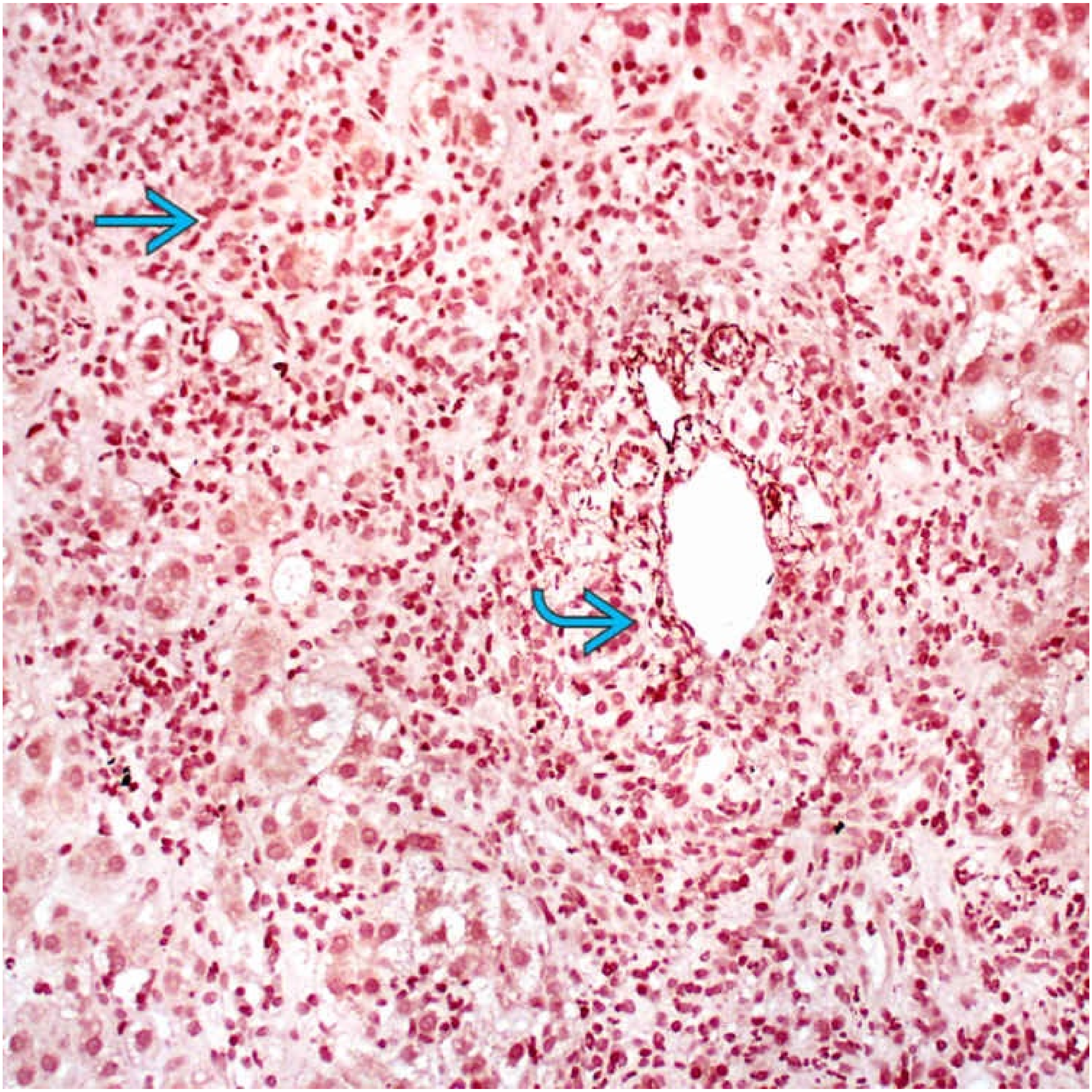
Necrosis and Ductular Reaction

Acute hepatitis showing confluent necrosis with inflammation → and ductular reaction ↪. The latter feature is a common accompaniment of confluent necrosis and does not indicate biliary disease in this setting.



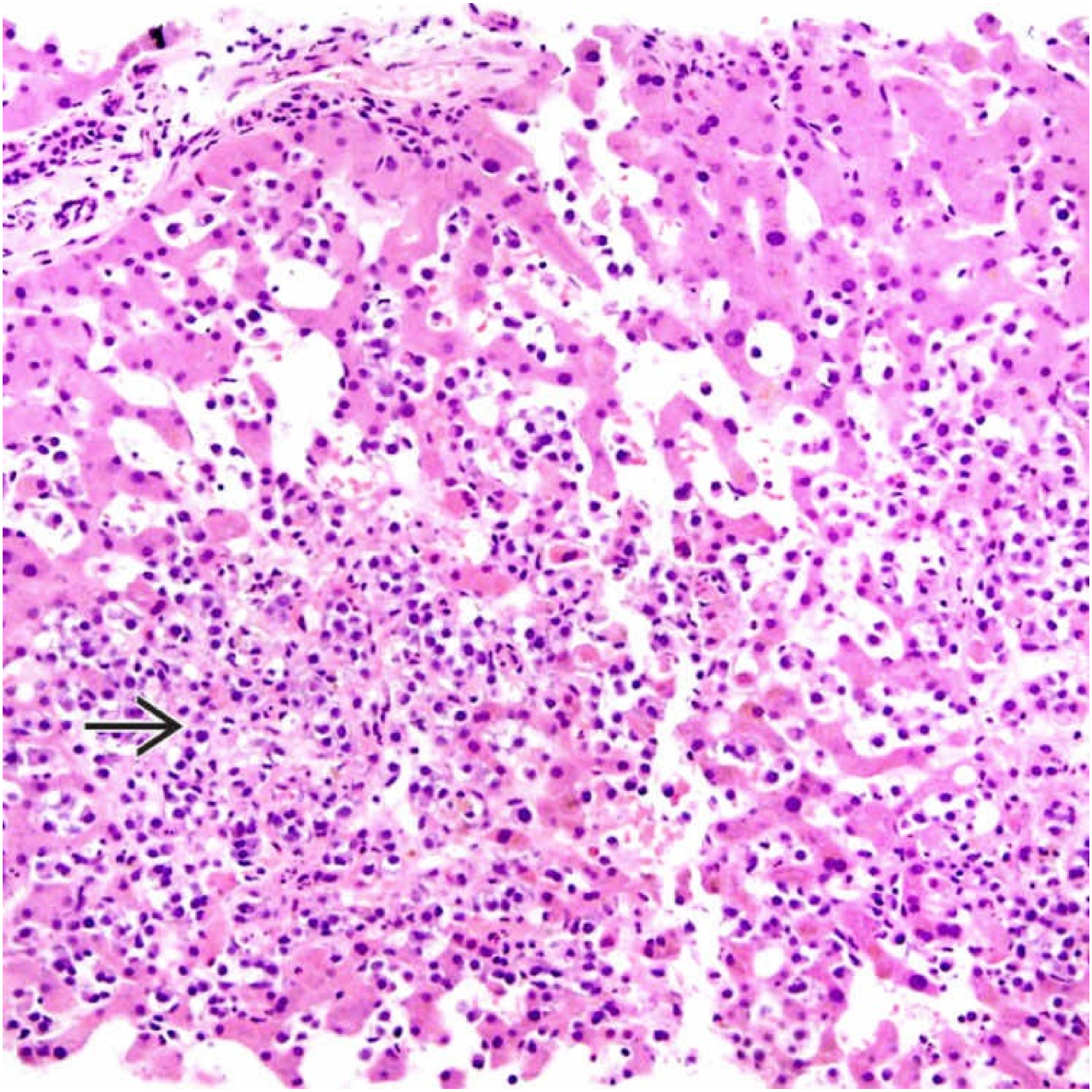
Regenerative Nodules

Trichrome stain shows pale staining in the areas of bridging necrosis → in contrast to the darkly stained collagen in the portal tract ⇨. Fibrous septa in cirrhosis would show darkly stained collagen similar to portal tracts.

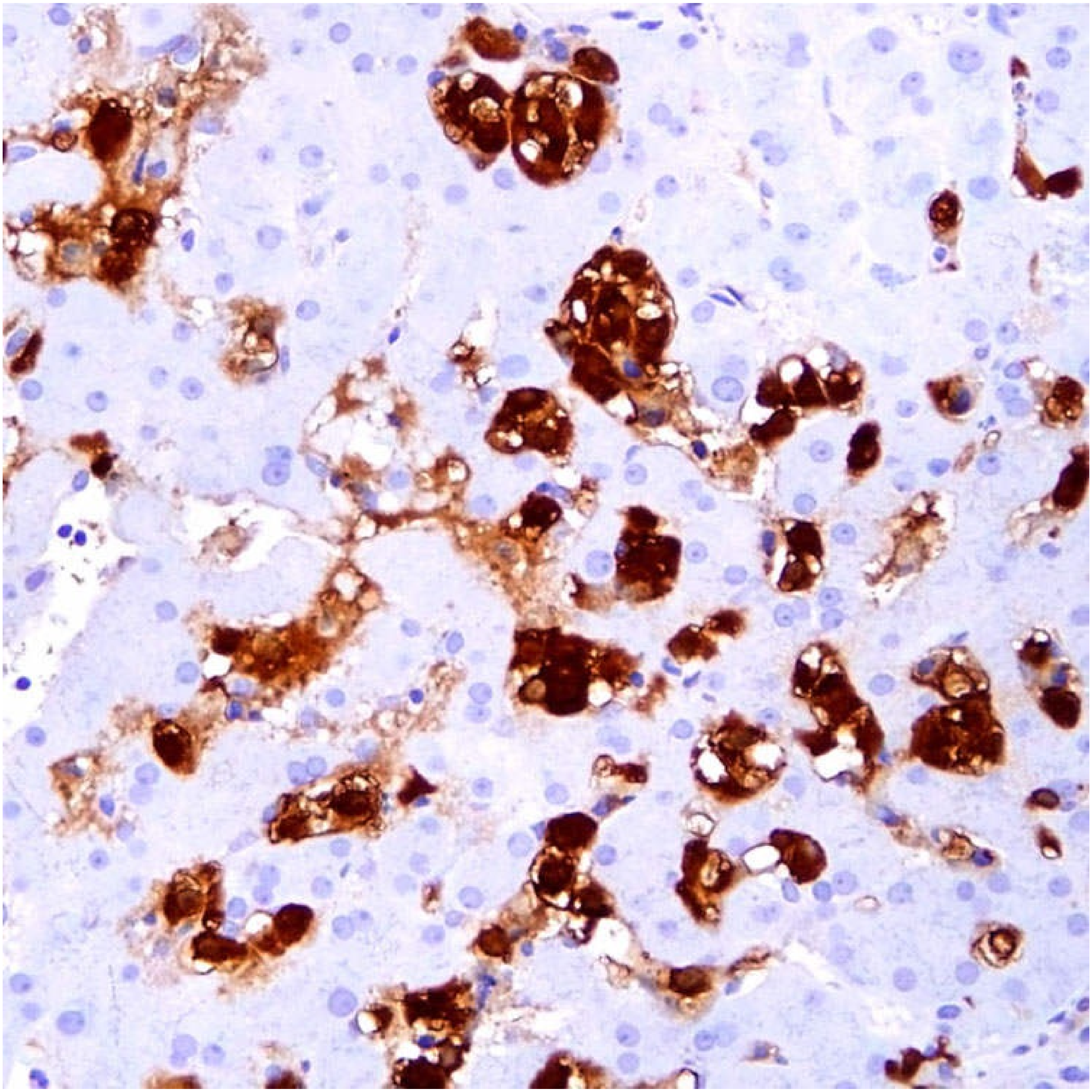


Orcein Stain

Orcein stain shows the absence of elastic fibers in the areas of confluent necrosis. Elastic fibers can be seen in the portal tracts, which serves as a useful internal control. Orcein works better in the liver to demonstrate elastic fibers compared to EVG stain.



Metastatic Malignant Melanoma
Hepatic sinusoids are extensively infiltrated by tumor cells →, leading to acute liver failure. Inflammation and necrosis are minimal.



Metastatic Malignant Melanoma
Immunohistochemistry for S100 highlights the infiltrating tumor cells in the sinusoids. HMB-45 and melan-A were also positive. Malignant melanoma with liver involvement is a rare cause of acute liver failure.

SELECTED REFERENCES

1. Hayashi, PH, et al. Clinical features, diagnosis, and natural history of drug-induced liver injury. *Semin Liver Dis*. 2014; 34(2):134–144.
2. Njoku, DB. Drug-induced hepatotoxicity: metabolic, genetic and immunological basis. *Int J Mol Sci*. 2014; 15(4):6990–7003.
3. Lee, NM, et al. Liver disease in pregnancy. *World J Gastroenterol*. 2009; 15(8):897–906.
6. Larson, AM, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. *Hepatology*. 2005; 42(6):1364–1372.

7. Schiødt, FV, et al. Viral hepatitis-related acute liver failure. *Am J Gastroenterol*. 2003; 98(2):448–453.
8. Ostapowicz, G, et al. S. Acute Liver Failure Study Group. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med*. 2002; 137(12):947–954.
10. Bhaduri, BR, et al. Fulminant hepatic failure: pediatric aspects. *Semin Liver Dis*. 1996; 16(4):349–355.
12. Powell-Jackson, PR, et al. Budd-Chiari syndrome presenting as fulminant hepatic failure. *Gut*. 1986; 27(9):1101–1105.

4. Korman, JD, et al. Screening for Wilson disease in acute liver failure: a comparison of currently available diagnostic tests. *Hepatology*. 2008; 48(4):1167–1174.
5. Polson, J, et al. False positive acetaminophen concentrations in patients with liver injury. *Clin Chim Acta*. 2008; 391(1-2):24–30.
9. Rowbotham, D, et al. Acute liver failure secondary to hepatic infiltration: a single centre experience of 18 cases. *Gut*. 1998; 42(4):576–580.
11. Williams, R. Classification, etiology, and considerations of outcome in acute liver failure. *Semin Liver Dis*. 1996; 16(4):343–348.

Drug-Induced Cholestatic Liver Injury

KEY FACTS

Etiology/Pathogenesis

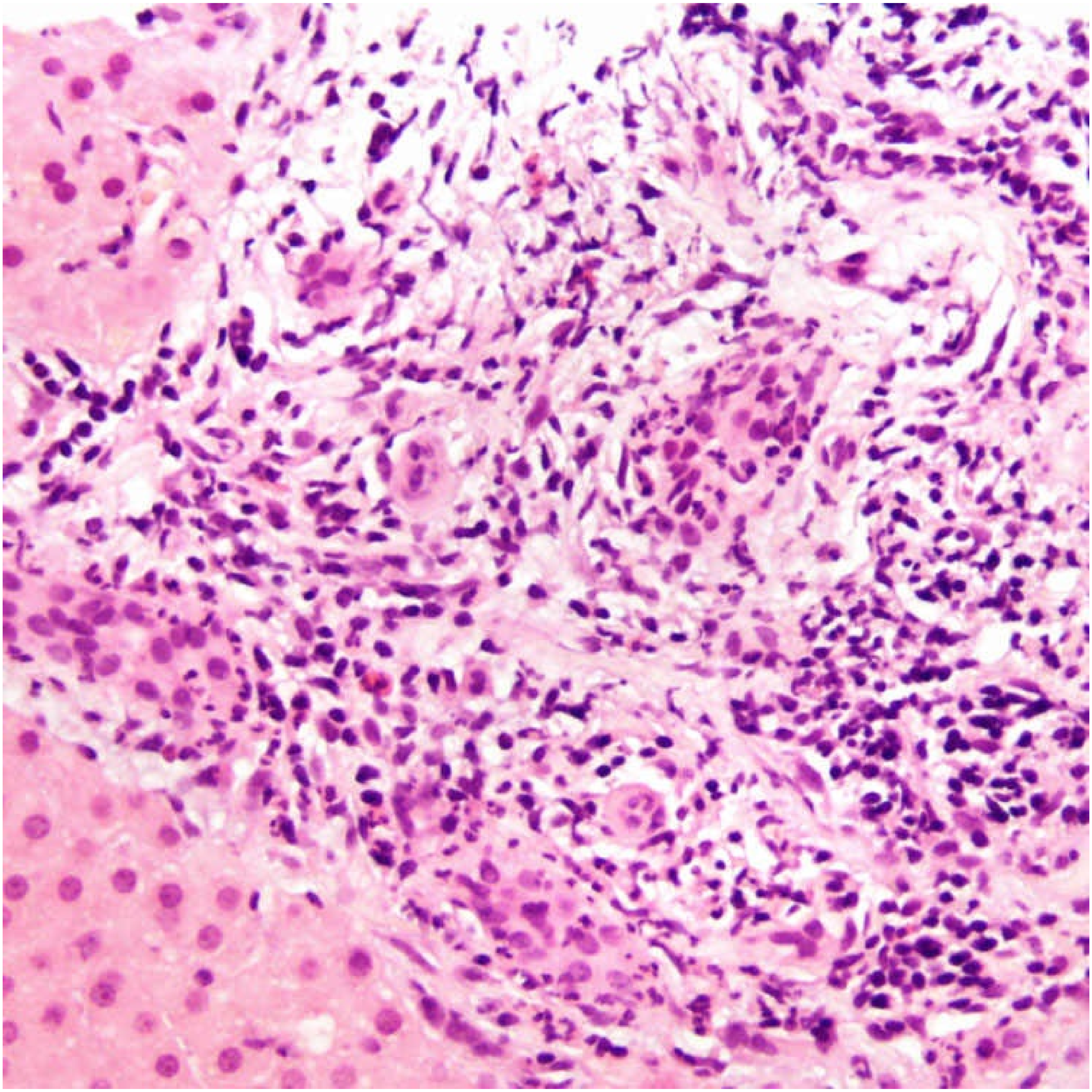
- Most common histologic pattern of drug-induced liver injury

Microscopic

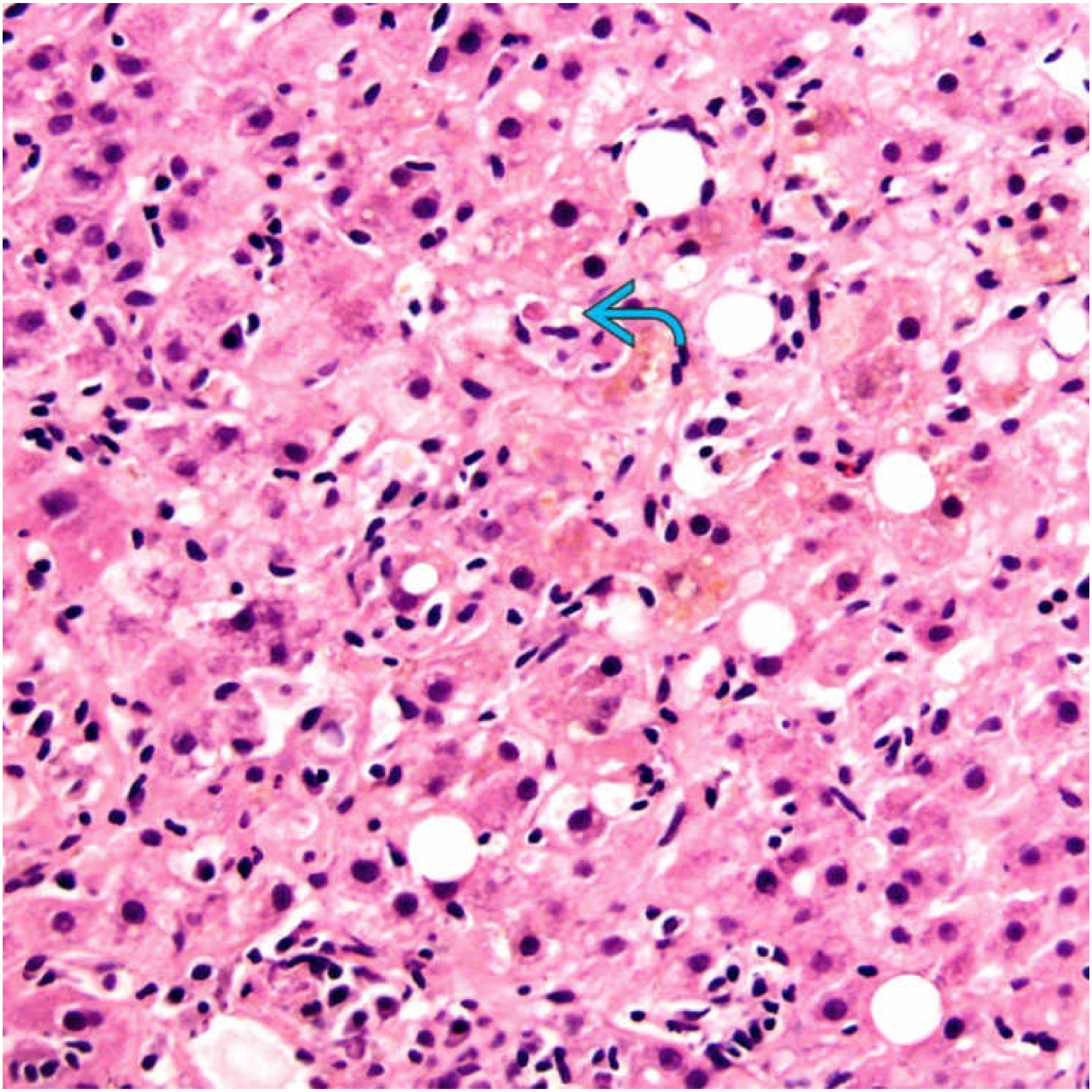
- Pure cholestasis: Cholestasis with minimal inflammation or hepatocellular damage
  - Commonly implicated drugs: Anabolic steroids, oral contraceptives, prochlorperazine, thiabendazole, warfarin
- Cholestatic hepatitis: Cholestasis with inflammation and hepatocellular damage
  - Macrolide antibiotics (erythromycin), antipsychotics (chlorpromazine), numerous other drugs
- Prolonged cholestasis/ductopenia: Cholestasis > 3 months, bile duct loss
  - Antibiotics, antifungals, anticonvulsants, antipsychotics, NSAIDs; rarely oral contraceptives, amiodarone
- Sclerosing duct injury: Fibrosis affecting large bile ducts similar to primary sclerosing cholangitis (PSC)
  - 5-fluorodeoxyuridine (intraarterial infusion for metastatic colorectal carcinoma), formaldehyde, and sodium chloride (injected into hydatid cysts)

Top Differential Diagnoses

- Pure cholestasis: Sepsis, shock, benign recurrent intrahepatic cholestasis
- Cholestatic hepatitis: Other causes of hepatitis (viral, autoimmune, Wilson disease)
- Obstructive biliary disease
- Prolonged cholestasis/ductopenia: Primary biliary cholangitis and PSC

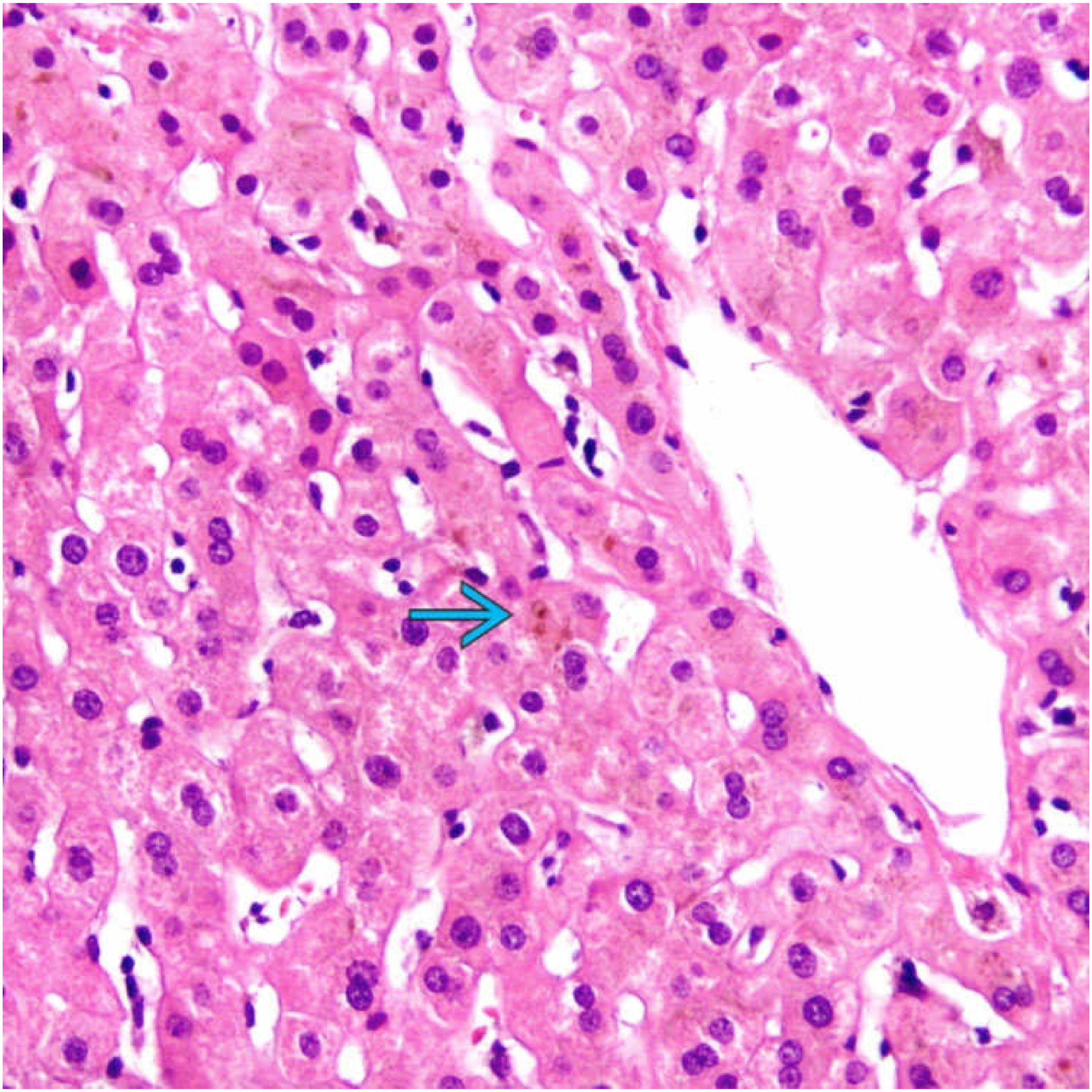


Obstruction-Like Features
Portal edema, inflammation, and bile ductular reaction in drug-induced liver injury (DILI) may be indistinguishable from obstructive biliary disease on histologic grounds.



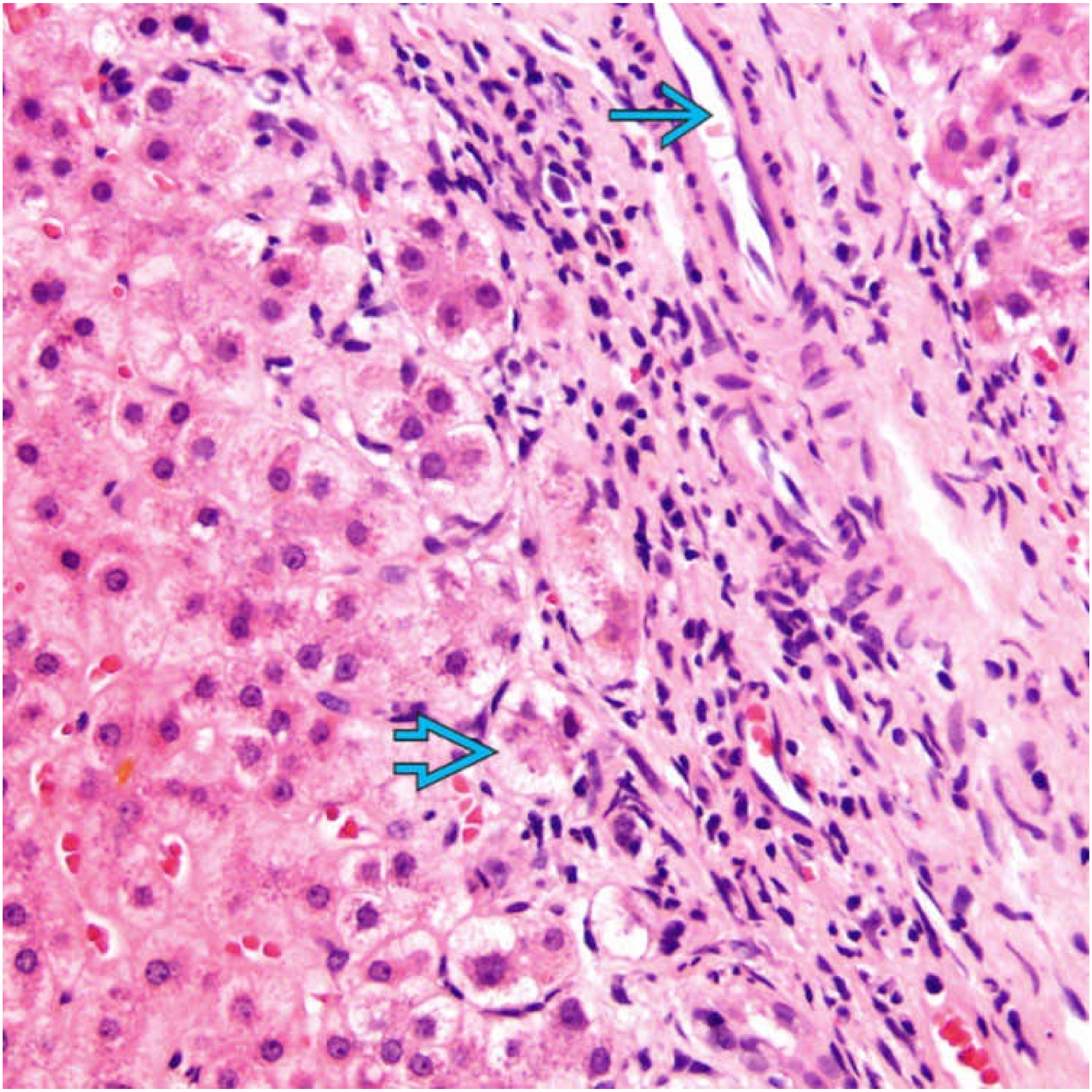
Cholestatic Hepatitis

Cholestasis is accompanied by hepatitic features evidenced by lobular inflammation and hepatocellular dropout. This is the most common histologic pattern observed in DILI.



Pure Cholestasis

This pattern, also known as bland cholestasis, is characterized by bile in hepatocytes and canaliculi → with no significant hepatocellular injury or inflammation. The portal tracts and interlobular bile ducts are normal and ductular reaction is not present in this pattern.



Prolonged Cholestasis
Arteriole without interlobular bile duct indicates bile duct loss →. Swelling of periportal hepatocytes is present ⇒ (cholate stasis), a feature of prolonged cholestasis.

TERMINOLOGY

Abbreviations

- Cholestatic drug-induced liver injury (DILI), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC)

ETIOLOGY/PATHOGENESIS

4 General Categories

- Based on symptom duration and histologic pattern of injury

Pure Cholestasis

- Cholestasis with minimal hepatocellular injury
- Commonly implicated drugs: Anabolic steroids, oral contraceptives, prochlorperazine, thiabendazole, warfarin

Cholestatic Hepatitis

- Most common pattern of DILI
- Cholestasis with hepatocellular injury
- Macrolide antibiotics (erythromycin), antipsychotics (chlorpromazine), numerous other drugs

Prolonged Cholestasis and Ductopenia

- Antibiotics, antifungals, anticonvulsants, antipsychotics, NSAIDs; rarely oral contraceptives, amiodarone

Sclerosing Bile Duct Injury

- 5-fluorodeoxyuridine (intraarterial infusion for metastatic colorectal carcinoma), formaldehyde, and sodium chloride (injected into hydatid cysts)

CLINICAL ISSUES

Presentation

- Jaundice, pruritus, dark urine, pale stools

Laboratory Tests

- Elevated alkaline phosphatase and GGT
- Transaminases minimally elevated in pure cholestasis; modest to marked elevation in cholestatic hepatitis

Prognosis

- Most cases resolve with cessation of offending drug
- Prolonged cholestasis (> 3 months) and ductopenia occurs in rare instances

MICROSCOPIC

Histologic Features

- Pure (bland) cholestasis
  - Bile plugs in hepatocytes &/or canaliculi
  - – Most prominent in centrizonal region
- Portal/lobular inflammation, bile ductular reaction, and hepatocellular injury are minimal or absent
- No bile duct damage
- Cholestatic hepatitis (cholangiolitic or hypersensitivity cholestasis)
  - Bile plugs in hepatocytes &/or canaliculi
  - Portal &/or lobular inflammation, predominantly lymphocytic, with variable plasma cells and eosinophils
  - Bile ductular reaction with associated neutrophilic infiltrate may be present
  - Bile duct epithelial injury and lymphocytic cholangitis may be present
    - – No ductopenia
  - Variable degree of hepatocellular injury ranging from isolated hepatocellular dropout to confluent necrosis
- Prolonged cholestasis (> 3 months) and ductopenia
  - Variable inflammation, bile duct injury, ductular reaction, and hepatocellular damage
  - Some cases progress to loss of bile ducts and overt ductopenia (vanishing bile duct syndrome)
  - Rare cases progress to cirrhosis
- Sclerosing bile duct injury
  - Fibrosis and strictures affecting extrahepatic and intrahepatic bile ducts similar to PSC

DIFFERENTIAL DIAGNOSIS

Pure Cholestasis

- Systemic disorders (sepsis, cardiac failure, shock)
- Postoperative cholestasis, intrahepatic cholestasis of pregnancy, benign recurrent intrahepatic cholestasis
- Clinical information is necessary to exclude these etiologies
- Early obstructive biliary disease can lack portal edema, ductular reaction, and inflammation, mimicking pure cholestasis

Cholestatic Hepatitis

- Autoimmune hepatitis, acute viral hepatitis, Wilson disease
  - Serological tests for hepatitis viruses, autoantibodies, and work-up for Wilson disease
- Obstructive biliary disease
  - Ductular reaction, bile duct injury, and cholestasis similar to cholestatic DILI
  - Imaging necessary to evaluate bile ducts
- PBC and PSC
  - Hepatocellular injury minimal or absent, transaminases modestly elevated (typically less than 300

U/L)
- Histological cholestasis in early disease (without fibrosis) does not occur in PBC and PSC
- Antimitochondrial antibodies (AMA) in PBC
- Characteristic abnormalities in large ducts on cholangiography in PSC

Prolonged Cholestasis and Vanishing Bile Duct Syndrome

• PBC and PSC: AMA and cholangiography essential to exclude these possibilities
• Rare causes of ductopenia: Ischemic bile duct injury, chronic hepatitis C

Sclerosing Bile Duct Injury

• Indistinguishable from PSC or secondary sclerosing cholangitis
• Cholangiography, drug history necessary to establish etiology

SELECTED REFERENCES

1. LiverTox. Cholestatic hepatitis. http://livertox.nih.gov/Phenotypes_chol.html. [Reviewed June 27, 2016. Accessed June 27, 2015.].
2. Padda, MS, et al. Drug-induced cholestasis. *Hepatology*. 2011; 53(4):1377–1387.
3. Ramachandran, R, et al. Histological patterns in drug-induced liver disease. *J Clin Pathol*. 2009; 62(6):481–492.
4. Levy, C, et al. Drug-induced cholestasis. *Clin Liver Dis*. 2003; 7(2):311–330.

Drug-Related Granulomatous Hepatitis

KEY FACTS

Terminology

- Granulomatous inflammation caused by drug or toxin
  - Drugs reportedly responsible for up to 30% of hepatic granulomas
- Drug-induced hepatic injury can mimic any other form of liver disease

Etiology/Pathogenesis

- Many types of offending drugs, including over-the-counter and herbal preparations
  - Antimicrobials
  - Anticonvulsants
  - Cardiac drugs (calcium channel blockers, antiarrhythmics)
  - Allopurinol

Clinical Issues

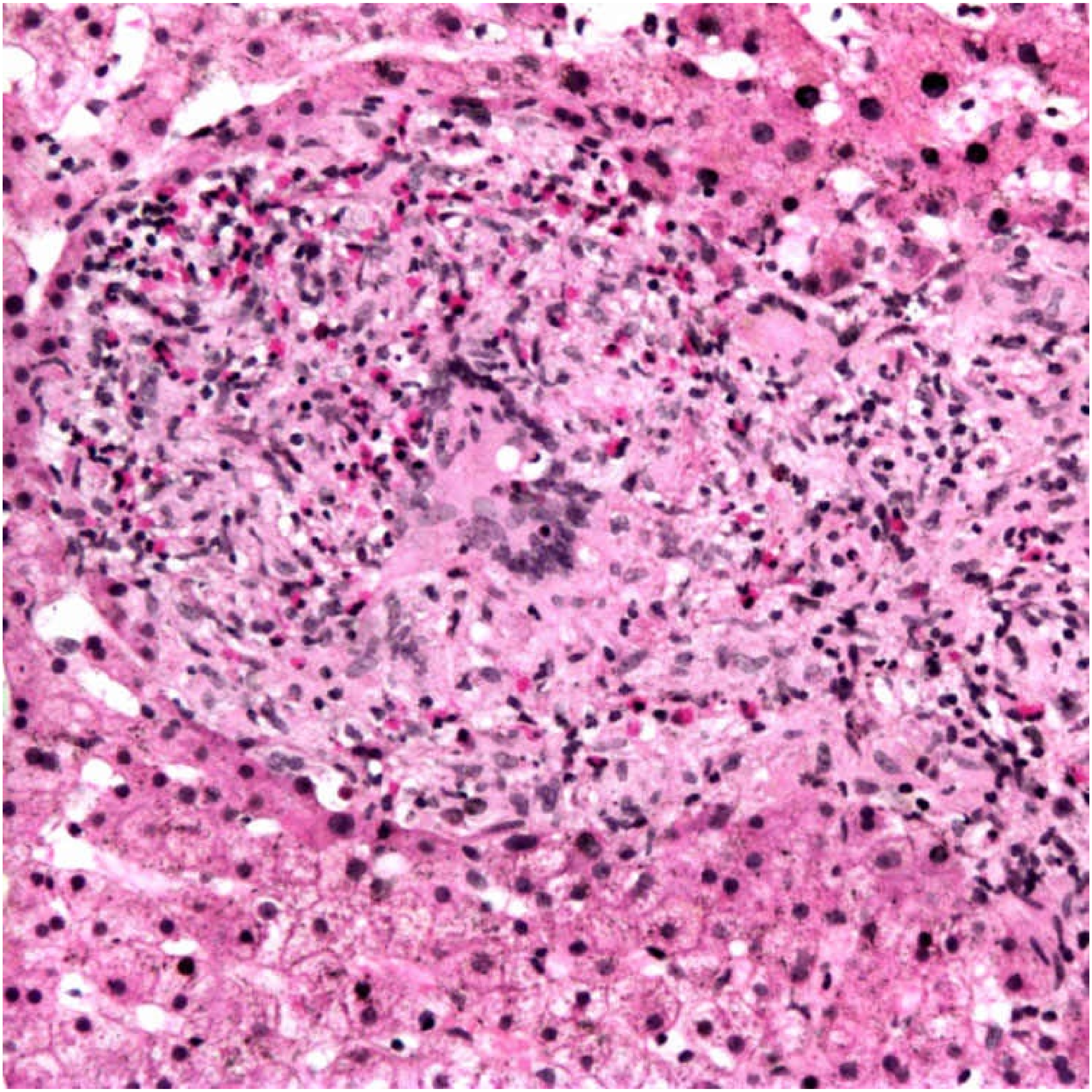
- Presentation varies with offending drug
  - ± signs and symptoms of hypersensitivity reaction
  - Elevated transaminases, sometimes markedly so
- Histology usually improves with cessation of offending drug

Microscopic

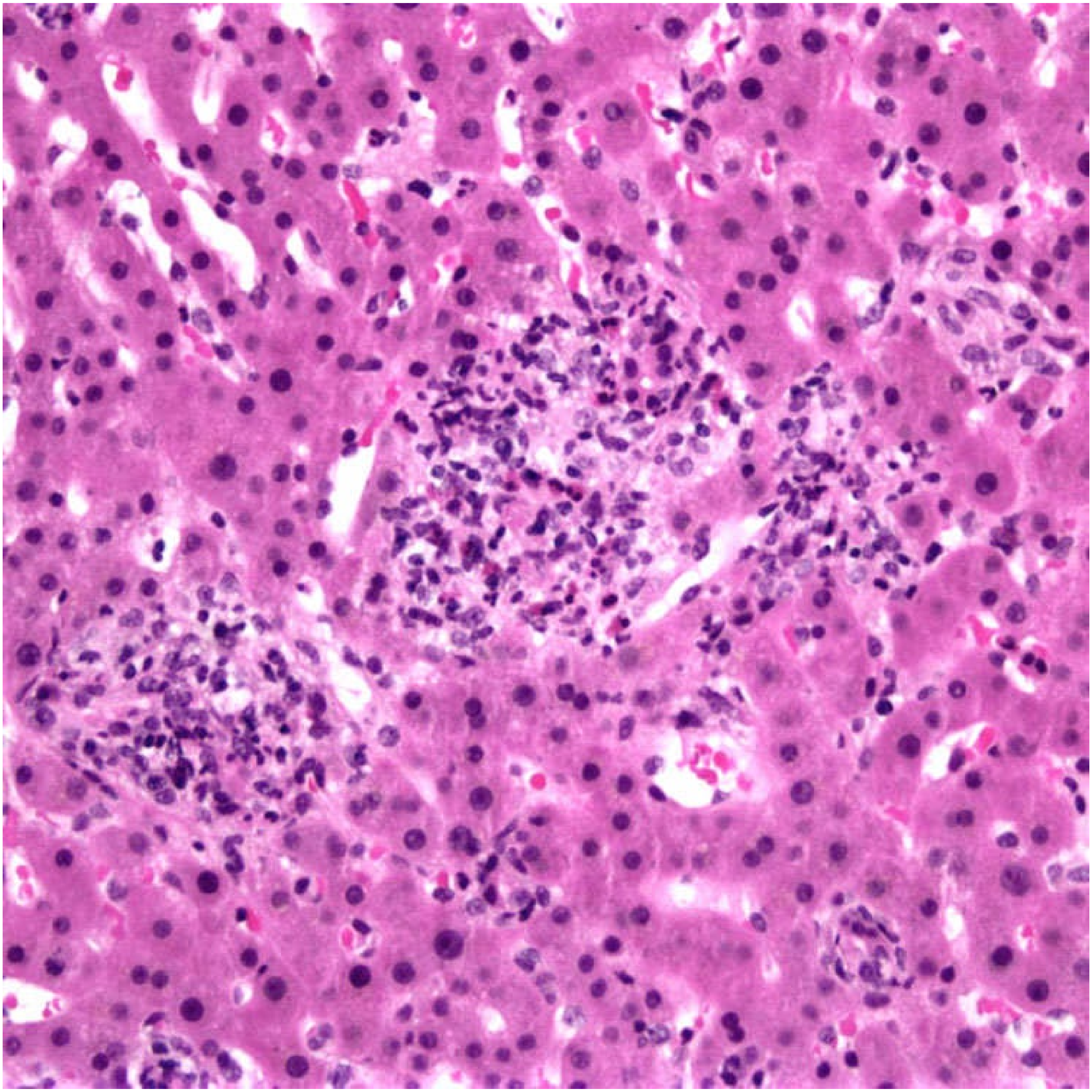
- Noncaseating granulomas
  - Often associated with lymphocytes, plasma cells, and (most notably) eosinophils
    - Presence of granulomas, ± eosinophils, does not prove drug-related etiology, however
  - Hepatocyte reactive changes, apoptotic hepatocytes, cholestasis, cytoplasmic ballooning/feathery degeneration may be present
    - Combination of microgranulomas and hepatocyte injury is very suggestive of granulomatous drug reaction

Diagnostic Checklist

- Careful drug history and temporal correlation between drug administration and liver disease are essential

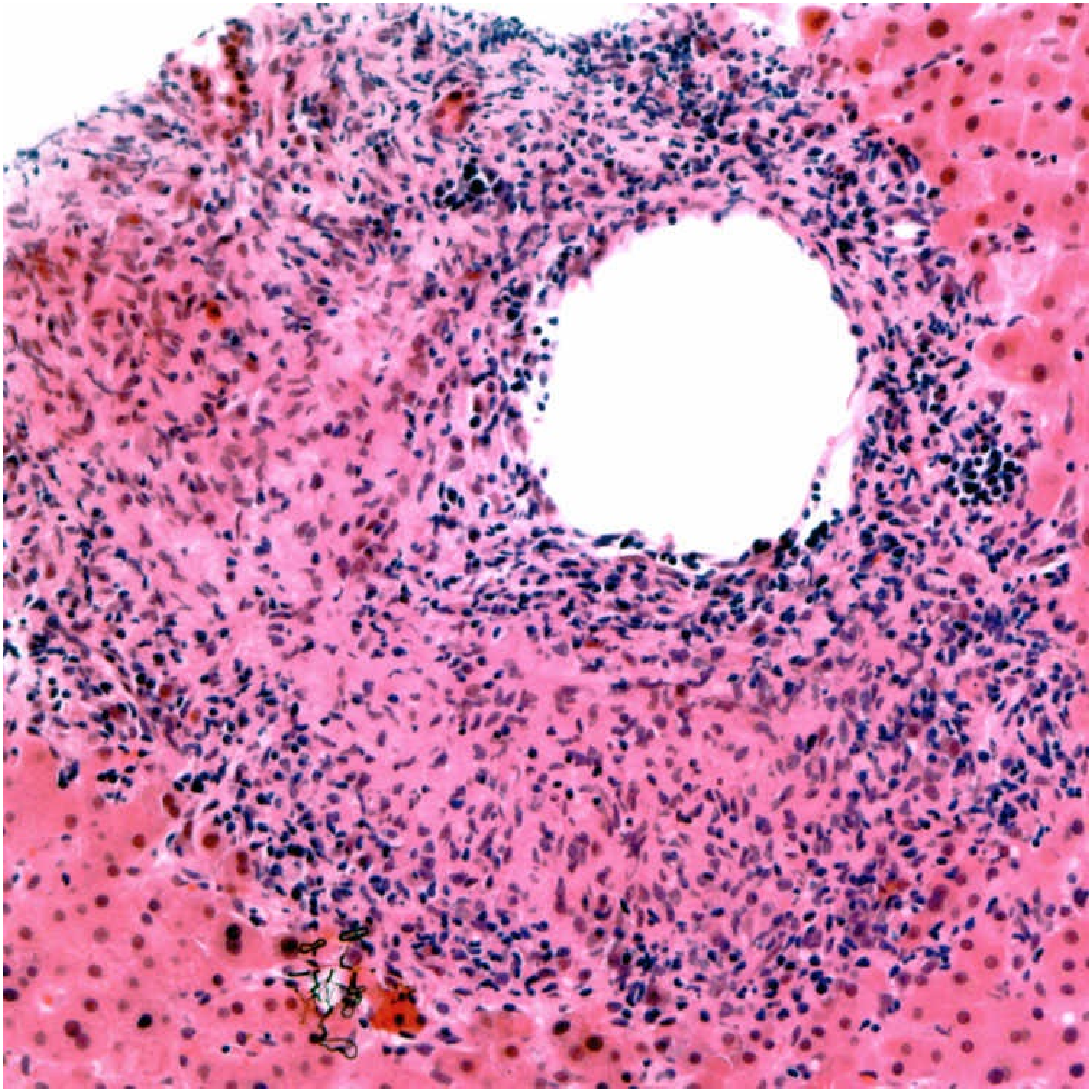


Epithelioid Granuloma With Eosinophils
This portal tract contains an epithelioid granuloma with numerous associated eosinophils, as well as a central giant cell. The patient’s granulomatous hepatitis was due to drinking Echinacea (coneflower) tea.

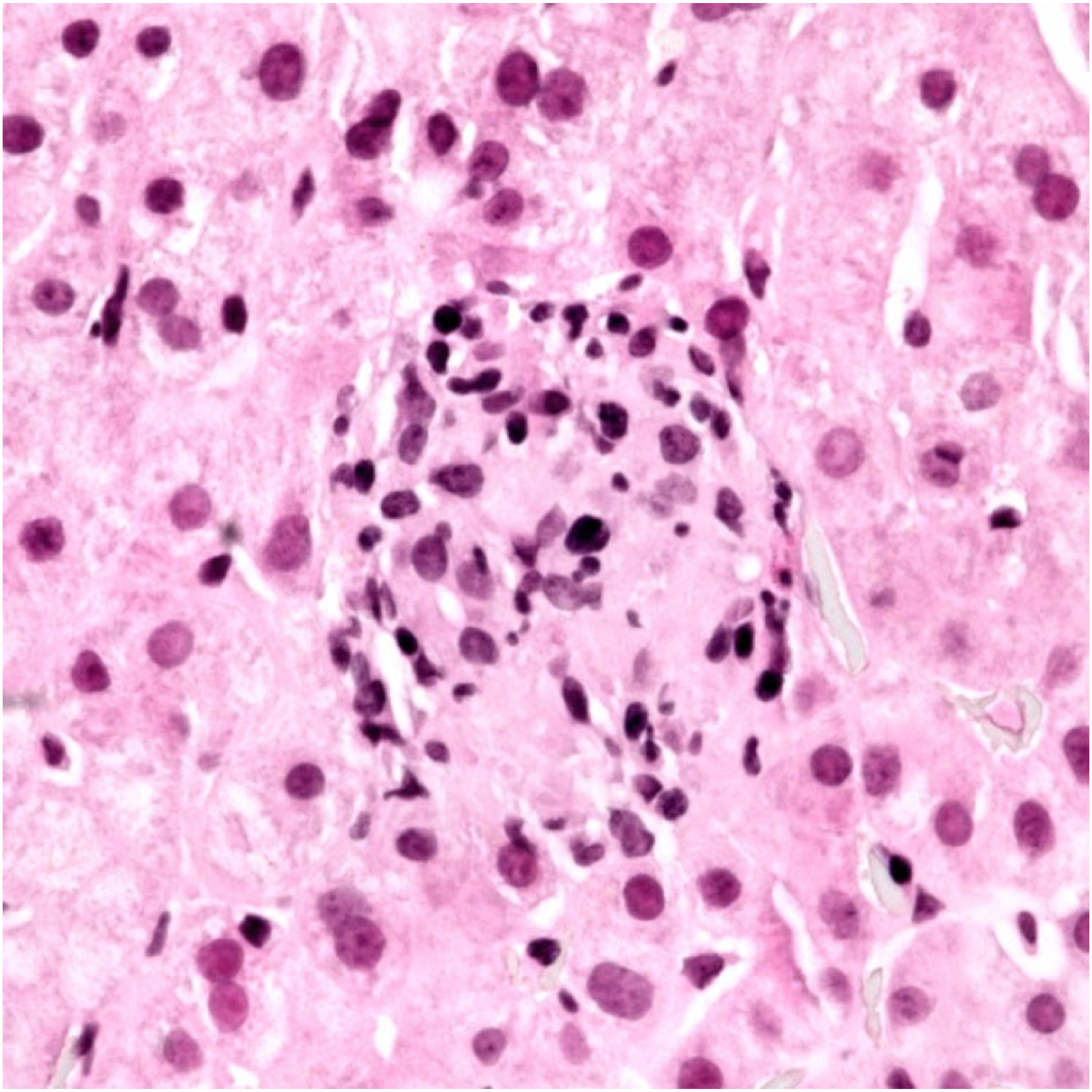


Microgranuloma

Microgranulomas, shown here with admixed lymphocytes and eosinophils, are often seen in drug reactions. This patient had a reaction to propylthiouracil. Microgranulomas are often accompanied by hepatocyte injury.



Granulomatous Vasculitis
Granulomatous vasculitis surrounding a central vein is seen in this case of granulomatous hepatitis due to allopurinol. (Courtesy J. Misdraji, MD.)



Small Portal Granuloma
A small portal epithelioid granuloma with associated lymphocytes is seen in this case of Tegretol-related granulomatous hepatitis.

TERMINOLOGY

Definitions

- Granulomatous inflammation caused by drug or toxin
  - Important mechanism of drug-related hepatotoxicity
  - Drugs reportedly responsible for up to 30% of hepatic granulomas
  - Many implicated drugs, including over-the-counter and herbal preparations

ETIOLOGY/PATHOGENESIS

Probable Hypersensitivity Reaction

- Common offenders
    - Antimicrobials
        - Penicillins
        - Sulfa drugs
        - Cephalexin
        - Sulfadoxine (antimalarial)
        - Dapsone (antibacterial)
        - Isoniazid
    - Anticonvulsants
        - Carbamazepine
        - Phenytoin
        - Carbamazepine
    - Cardiac drugs
        - Diltiazem (calcium channel blocker)
        - Procainamide (antiarrhythmic)
        - Trichlormethiazide (diuretic)
    - Other
        - Allopurinol (antihyperuricemic)
        - Diazepam (benzodiazepine)
        - Glyburide (hypoglycemic)
        - Gold (antiarthritic)
        - Interferon
        - Procarbazine (antineoplastic)
        - Propylthiouracil (antithyroidal)

CLINICAL ISSUES

Presentation

- Varies with offending drug
    - Fever
    - Hepatomegaly
    - Clinical signs of hypersensitivity
        - Rash
        - Lymphadenopathy

- Drug-induced hepatic injury can mimic any other form of liver disease
- Some patients are asymptomatic

Laboratory Tests

- Elevated transaminases, sometimes markedly so
- Elevated alkaline phosphatase
- Variably elevated bilirubin
- May have peripheral eosinophilia
- May have hypergammaglobulinemia
- Variably present autoantibodies

Treatment

- Remove offending drug
- Steroids may be necessary

Prognosis

- Histology usually improves with cessation of offending drug
  - Usually does not result in progressive liver disease or fibrosis if drug is stopped

MICROSCOPIC

Histologic Features

- Vary with implicated drug
  - Noncaseating granulomas
    - Vary in number and size
    - May be compact or loose
    - Both portal and lobular
    - Granulomas associated with lymphocytes, plasma cells, and (most notably) eosinophils
    - Multinucleate giant cells often present
  - Fibrin ring granulomas may be seen with allopurinol
- Unless eosinophils are present, very difficult to distinguish drug-induced granulomas from granulomas of other causes
  - However, presence of granulomas, ± eosinophils, does not prove drug-related etiology
- Granulomas may be sole alteration or accompanied by
  - Hepatocyte reactive changes
  - Apoptotic hepatocytes
  - Steatosis
  - Cholestasis
  - Cytoplasmic ballooning
  - Cholangitis (usually associated with portal granulomas)
  - Vasculitis

DIFFERENTIAL DIAGNOSIS

Sarcoidosis

- Abnormal chest x-ray, elevated serum angiotensin-converting enzyme (ACE) favor sarcoidosis

Infection

- Special stains, immunohistochemistry, microbiological cultures useful to exclude infection

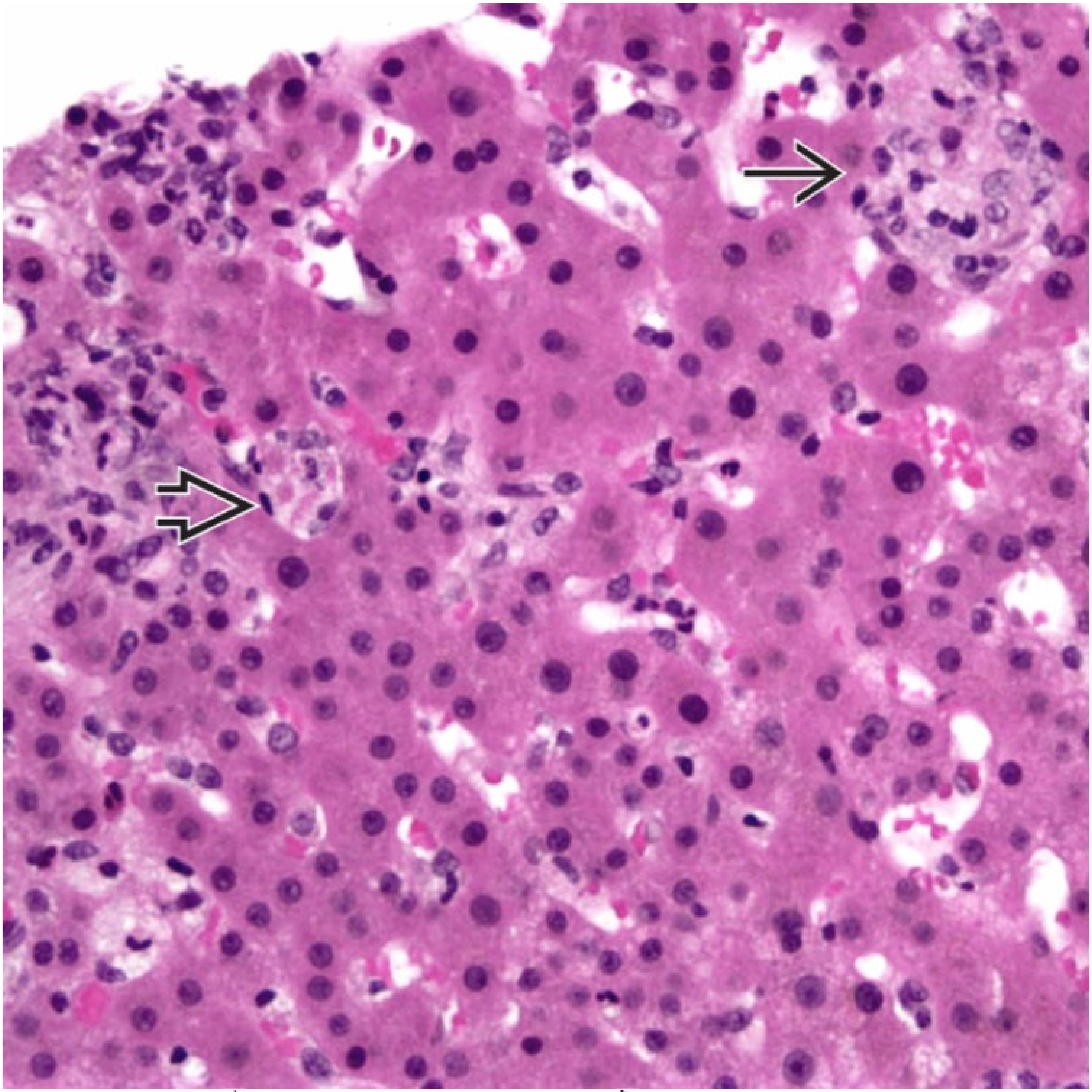
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

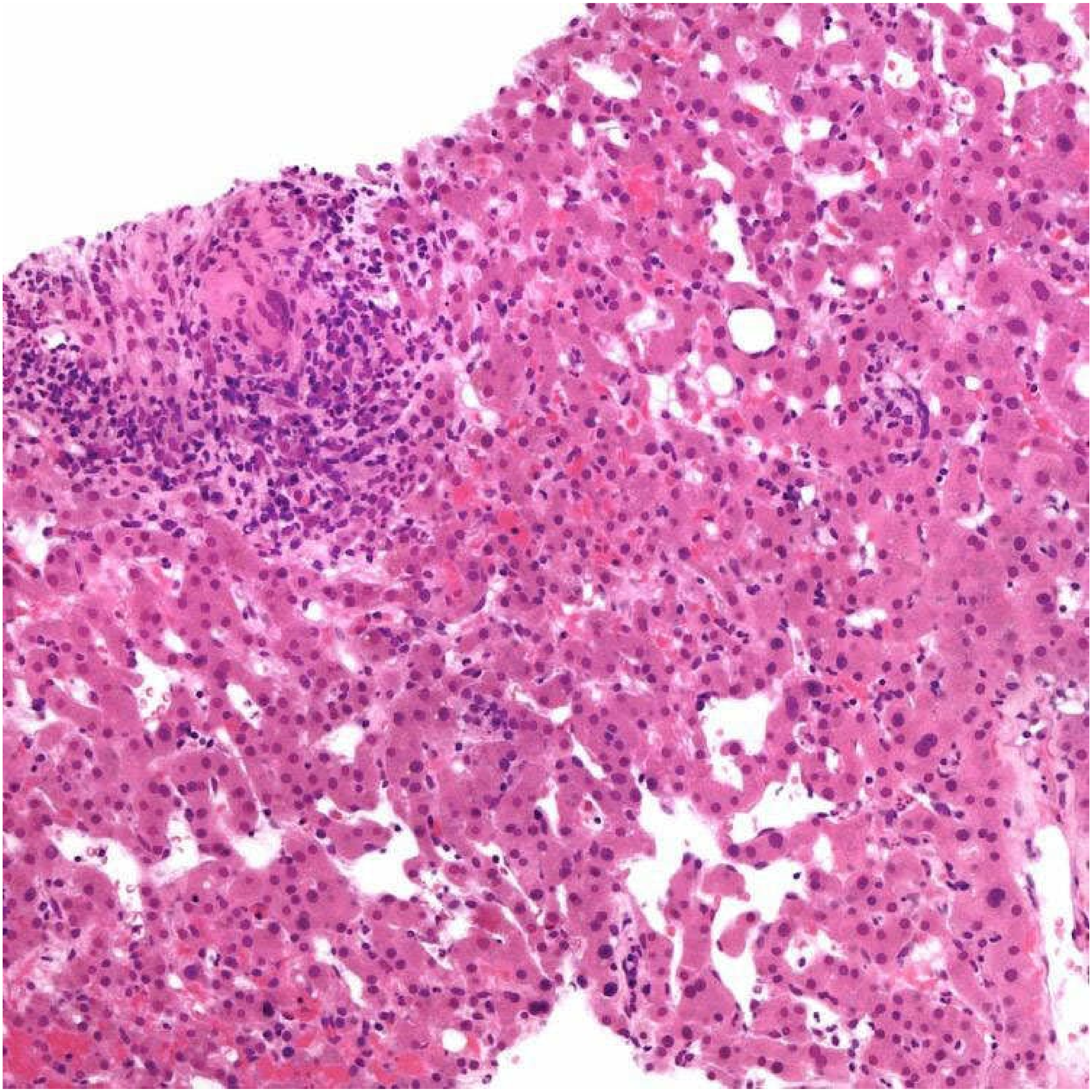
- Diagnosis requires high level of suspicion
- Need careful drug history and temporal correlation between drug administration and liver disease

Pathologic Interpretation Pearls

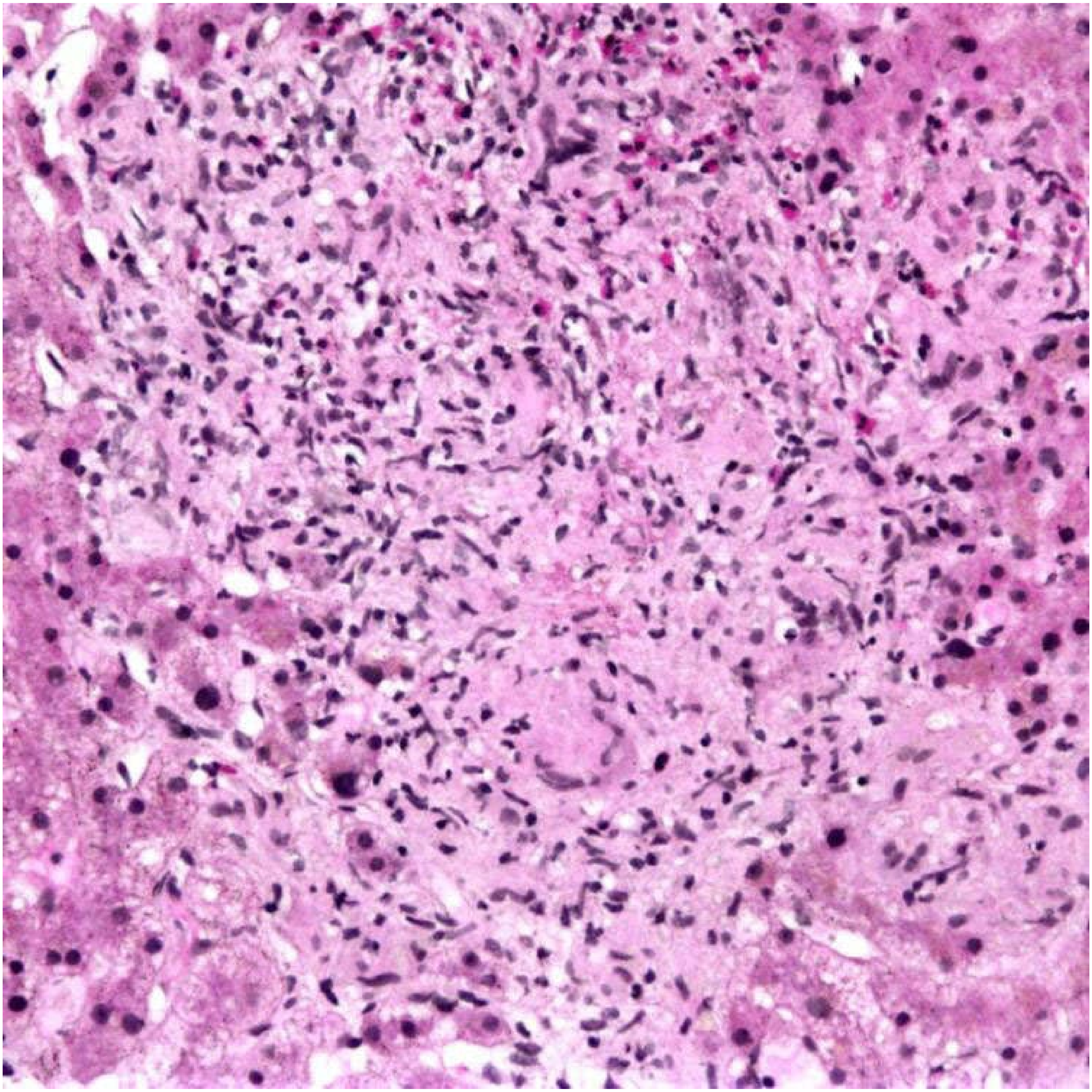
- Combination of microgranulomas and hepatocyte injury is very suggestive of granulomatous drug reaction



A microgranuloma → with associated apoptotic hepatocytes ⇨ and lobular inflammation is seen in a case of granulomatous drug reaction secondary to propylthiouracil.



An epithelioid portal granuloma is seen in a case of allopurinol toxicity. (Courtesy J. Misdraji, MD.)



An expansile portal granuloma with admixed lymphocytes and eosinophils is seen in a patient with granulomatous hepatitis secondary to ingestion of coneflower tea.

SELECTED REFERENCES

1. Ramachandran, R, et al. Histological patterns in drug-induced liver disease. *J Clin Pathol*. 2009; 62(6):481–492.
2. Wainwright, H. Hepatic granulomas. *Eur J Gastroenterol Hepatol*. 2007; 19(2):93–95.
3. Kleiner, DE. Granulomas in the liver. *Semin Diagn Pathol*. 2006; 23(3-4):161–169.
4. Anderson, CS, et al. Hepatic granulomas: a 15-year experience in the Royal Adelaide Hospital. *Med J Aust*. 1988; 148(2):71–74.
5. Al-Kawas, FH, et al. Allopurinol hepatotoxicity. Report of two cases and review of the literature. *Ann Intern Med*. 1981; 95(5):588–590.

6.Irani, SK, et al. Hepatic granulomas: review of 73 patients from one hospital and survey of the literature. *J Clin Gastroenterol*. 1979; 1(2):131–143.

Drug-Related Steatohepatitis/Phospholipidosis

KEY FACTS

Terminology

- Drug-induced steatohepatitis or phospholipidosis (intracellular accumulation of phospholipids)

Etiology/Pathogenesis

- Commonly implicated drugs
  - Amiodarone
  - Methotrexate
  - Antiretroviral drugs
  - Nifedipine

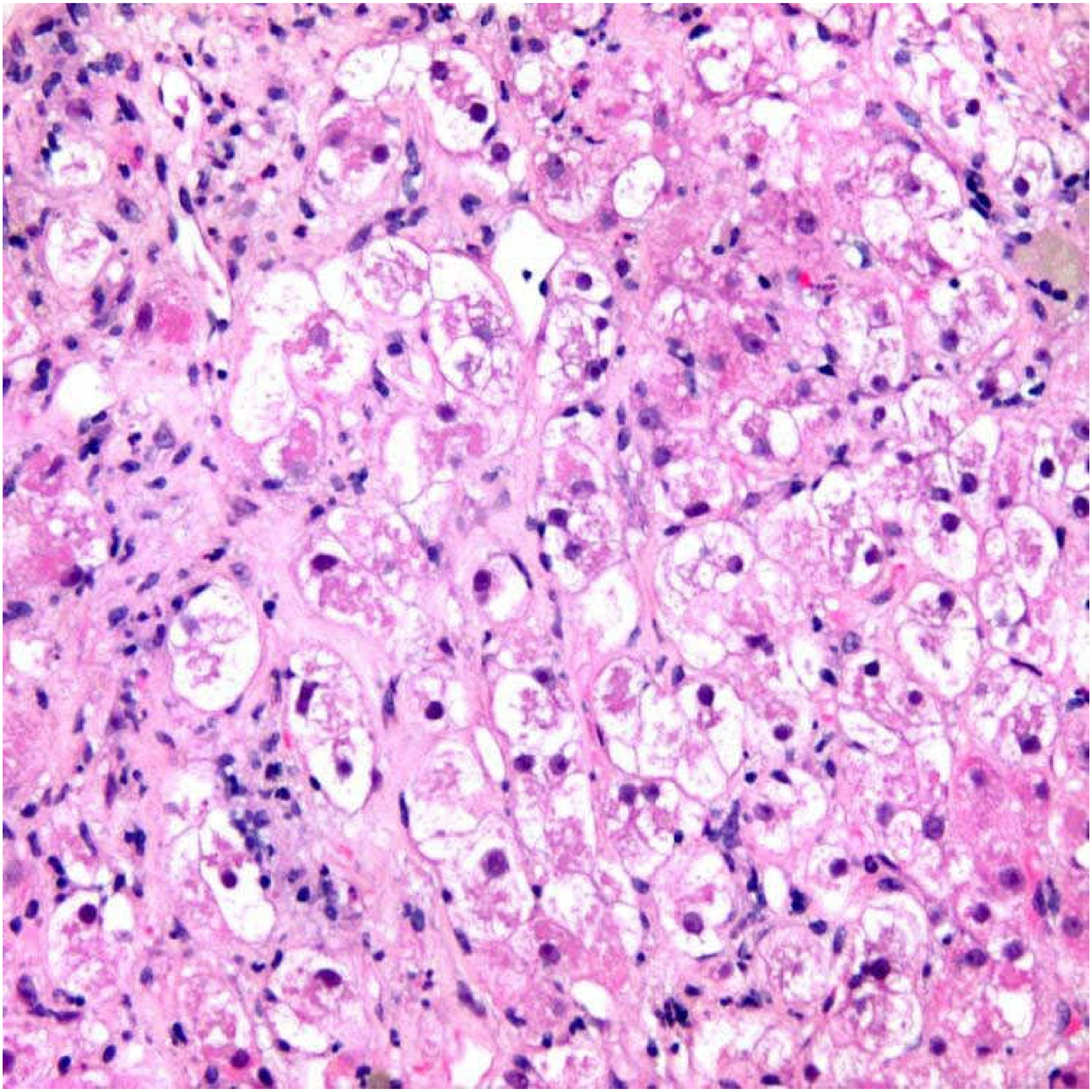
Clinical Issues

- Symptoms may present after months to years of therapy
  - Patients may be asymptomatic despite liver injury
- Due to long half-life of amiodarone, may take months to see improvement
- Risk of liver damage with methotrexate use depends on duration of therapy and dose
  - Exacerbated by concomitant obesity, alcohol use
- Patients with drug-induced phospholipidosis often also have history of alcohol use or risk factors for nonalcoholic steatohepatitis, confounding clinical picture

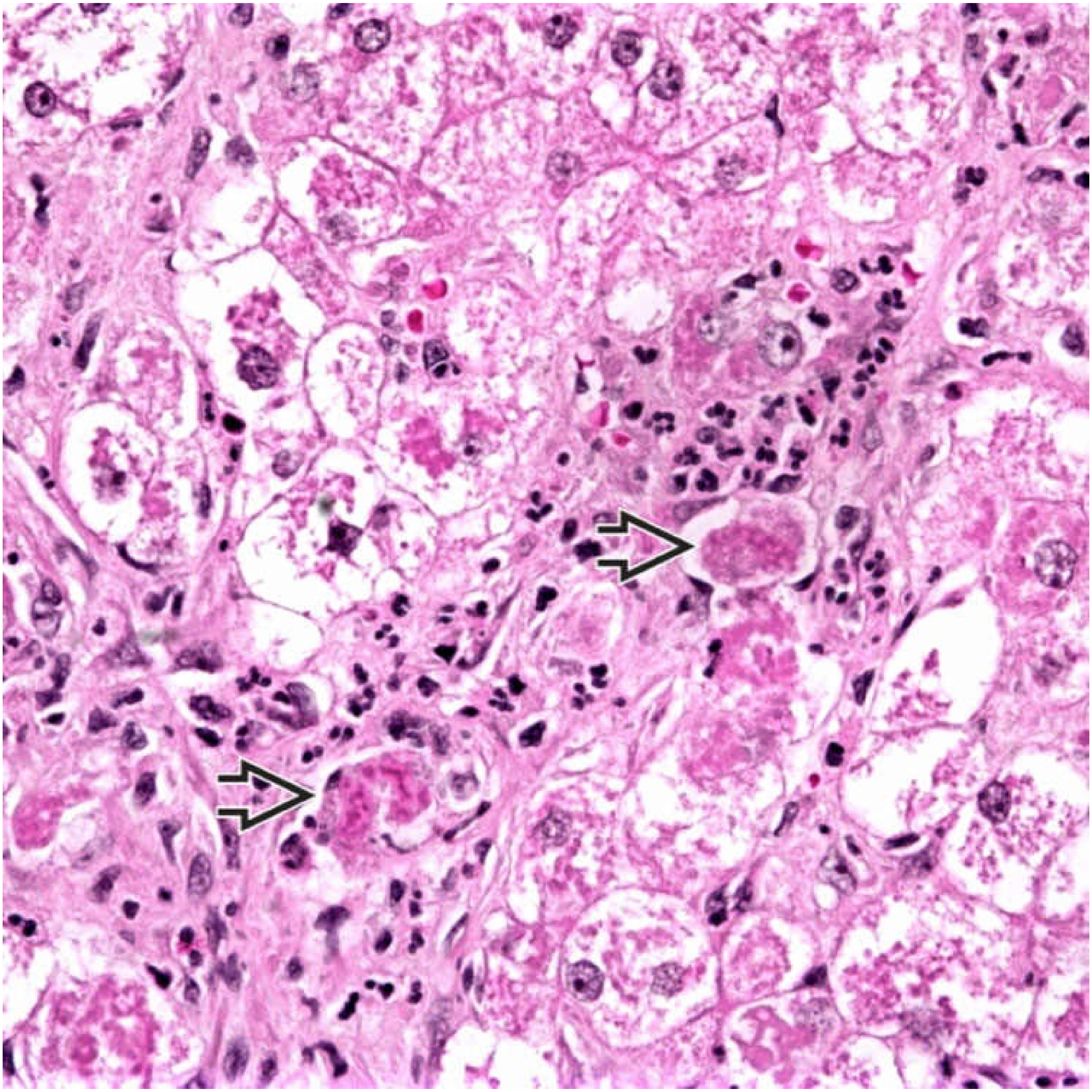
Microscopic

- Amiodarone
  - Steatosis
  - Phospholipidosis
  - Mallory hyaline, often with associated neutrophils (satellitosis)
- Methotrexate
  - Steatosis
  - Reactive changes
  - Fibrosis

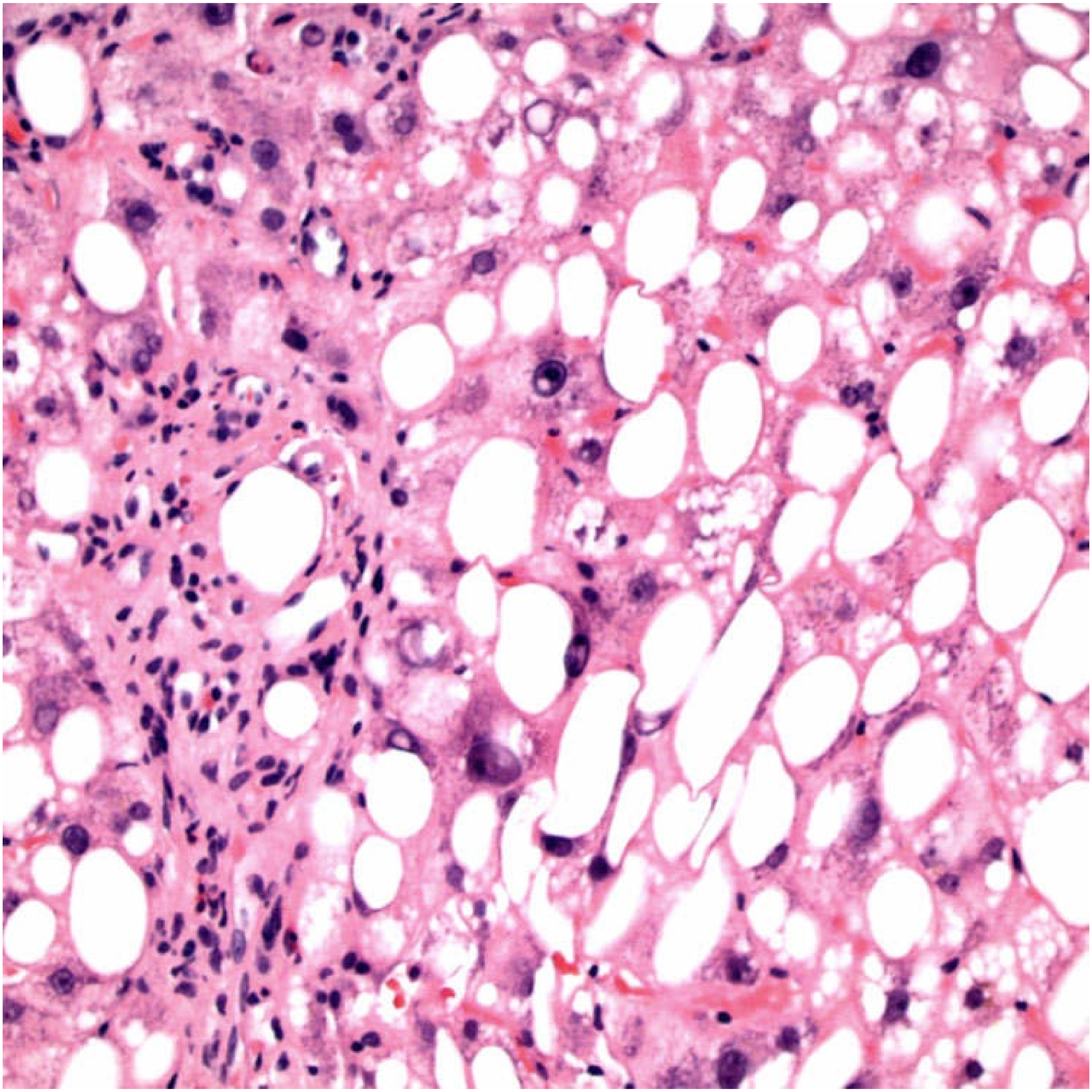
- Grading scheme exists for purposes of clinical decision making
  - Grades I-IV; drug usually stopped at IIIB-IV



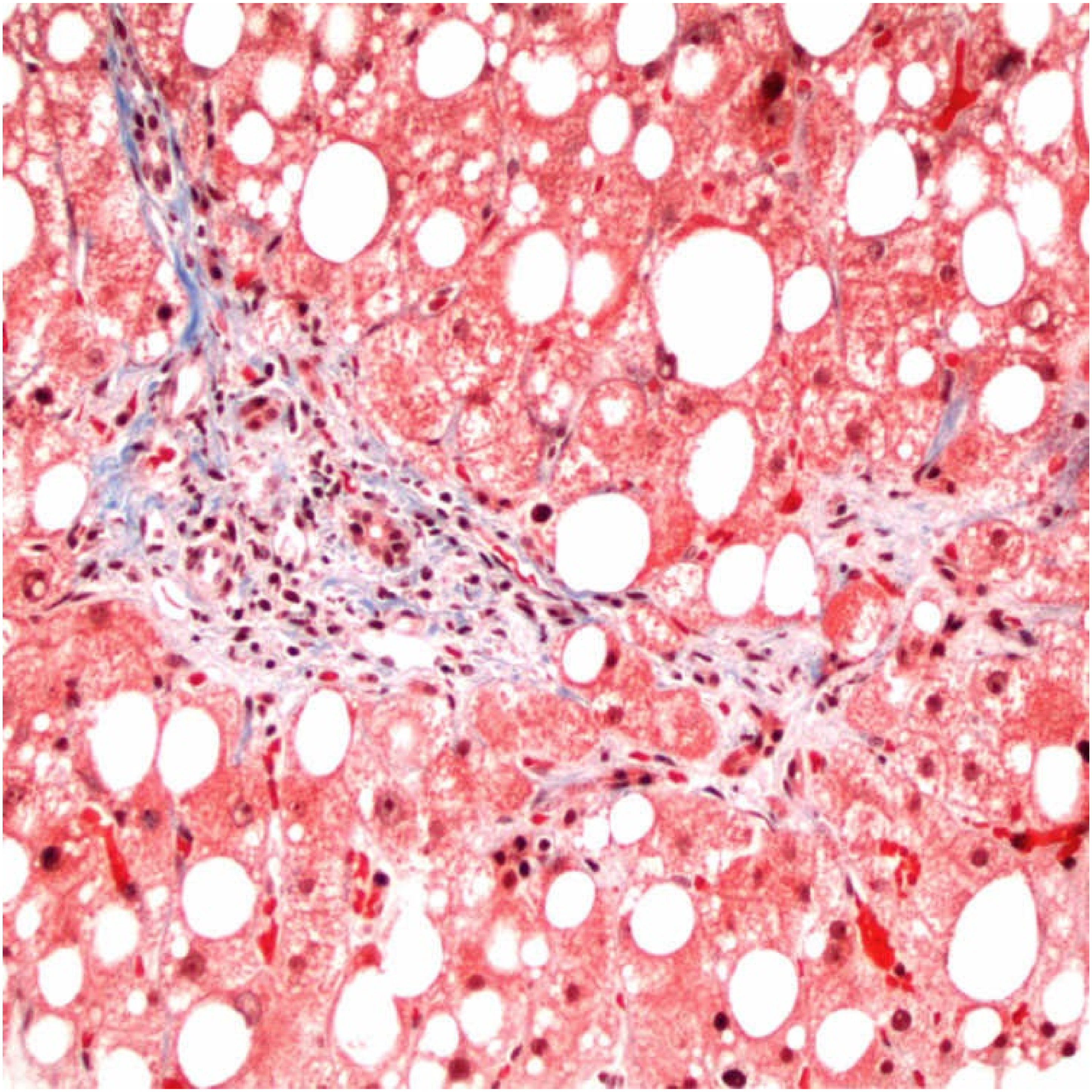
Amiodarone, Ballooned Hepatocytes
Amiodarone toxicity typically features ballooned hepatocytes with abundant Mallory hyaline.



Amiodarone, Mallory Hyaline and Satellitosis of Neutrophils
Features of amiodarone hepatotoxicity include foamy, ballooned hepatocytes and abundant Mallory hyaline ⇨ with surrounding neutrophils (satellitosis).



Methotrexate, Steatosis
Both macrovesicular and microvesicular steatosis can be seen in methotrexate injury. Inflammation may not be prominent.



Periportal Fibrosis
Trichrome stain shows delicate spurs of periportal fibrosis, as well as steatosis, in methotrexate toxicity.

TERMINOLOGY

Definitions

- Drug-induced steatohepatitis &/or phospholipidosis (intracellular accumulation of phospholipids)
  - Phospholipidosis likely from impaired phospholipid metabolism, although exact mechanism unknown

ETIOLOGY/PATHOGENESIS

Commonly Implicated Drugs

- Amiodarone (antiarrhythmic): Strongly tissue-bound, becomes concentrated in liver
  - Nifedipine (calcium channel blocker)
  - Perhexiline maleate (calcium channel blocker)
  - Methotrexate (immunosuppressant/antineoplastic): Hepatic injury usually occurs after long-term use
  - Tamoxifen (estrogen antagonist)
  - Steroids
  - Naproxen (NSAID)
  - Trimethoprim-sulfa (antibiotic)
  - Total parenteral nutrition
  - Anti-HIV drugs
  - Induce syndrome of dyslipidemia, fat maldistribution, insulin resistance
  - Known as HIV-associated lipodystrophy syndrome or HIV-associated metabolic and morphological abnormality syndrome (HAMMAS)

CLINICAL ISSUES

Presentation

- Variably present constitutional complaints, hepatomegaly, jaundice
  - May be asymptomatic (especially methotrexate injury)
- Symptoms may present after months to years of therapy

Laboratory Tests

- Elevated transaminases
  - May be normal despite hepatic injury, especially in patients on methotrexate

Prognosis

- Amiodarone
  - Cessation of therapy should lead to regression of injury
  - Due to long half-life of drug, may take months to see improvement
  - If drug is not withdrawn, process can progress to cirrhosis, hepatic failure
- Methotrexate
  - Risk of liver damage depends on duration of therapy and dose
  - Exacerbated by concomitant obesity, alcohol use
  - May progress to fibrosis or cirrhosis
  - Periodic liver biopsy recommended for surveillance

MICROSCOPIC

Histologic Features

- Amiodarone and other drugs causing phospholipidosis
  - Phospholipidosis: Granular, foamy appearance of hepatocytes corresponding to lamellar lysosomal inclusions by EM

– Corresponds to entrapment of amiodarone in lysosomes, with subsequent binding of phospholipids

- Hepatocyte swelling
- Abundant Mallory hyaline

– Often with associated neutrophils known as satellitosis

– Occasionally, abundant Mallory hyaline but fatty changes absent

- Steatosis
- Fibrosis/cirrhosis with progressive disease

• Methotrexate
  - Steatosis
    – Usually macrovesicular, but occasionally microvesicular
    – Variably present hypertrophic Ito cells
  - Nonspecific reactive changes
    – Hyperchromasia and anisocytosis of hepatocyte nuclei
    – Spotty hepatocyte necrosis with associated Kupffer cells
  - Portal inflammation
  - Fibrosis
    – Begins as irregular periportal spurs and progresses to portal/portal and portal/central bridging
    – Pericellular fibrosis may also be present
  - Grading scheme exists for purposes of clinical decision making
    – Grade I: Normal or only mild fatty or reactive changes
    – Grade II: Moderate to severe fatty or reactive changes
    – Grade III: Mild periportal fibrosis (IIIA) or moderate to marked fibrosis (IIIB)
    – Grade IV: Cirrhosis
  - Methotrexate should be stopped in IIIB or IV cases; cautiously continued with rebiopsy in 6 months in IIIA biopsies

DIFFERENTIAL DIAGNOSIS

Alcoholic Hepatitis

• History of alcohol use vs. history of offending drug

Nonalcoholic Steatohepatitis

• Often lacks abundant Mallory bodies
• Risk factors for nonalcoholic steatohepatitis vs. history of offending drug

Niemann-Pick Disease

• Hereditary disorder of lipid metabolism (diminished sphingomyelinase activity)
• May mimic amiodarone-induced phospholipidosis

Preexisting Hepatitis Treated With Steroids

- Most commonly seen in treated autoimmune hepatitis
  - Autoimmune serologies, medication history help to distinguish from drug-related steatohepatitis

Wilson Disease

- Abnormal ceruloplasmin, copper studies

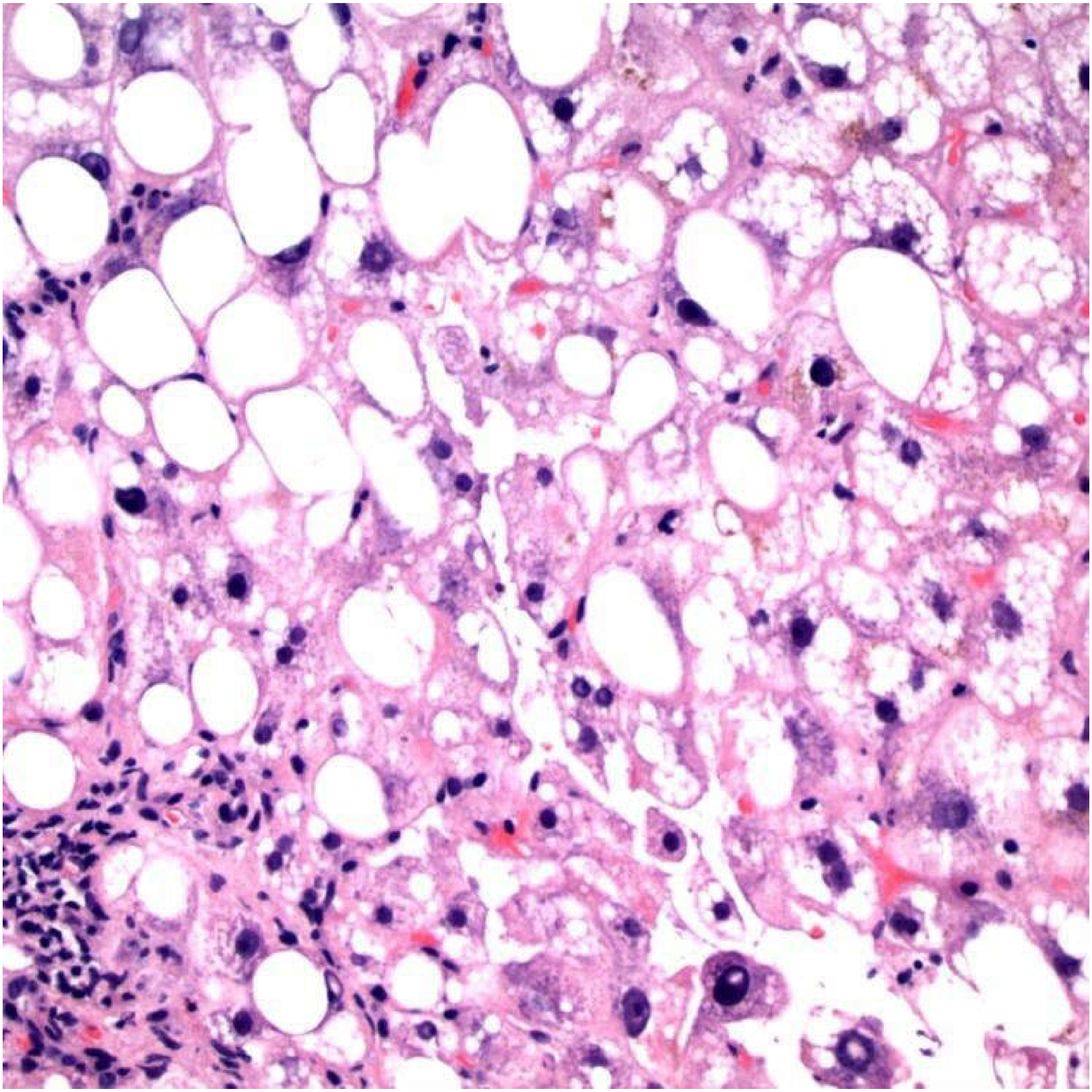
Malabsorption/Malnutrition

- History of malnutrition vs. history of offending drug
- Often lacks abundant Mallory hyaline

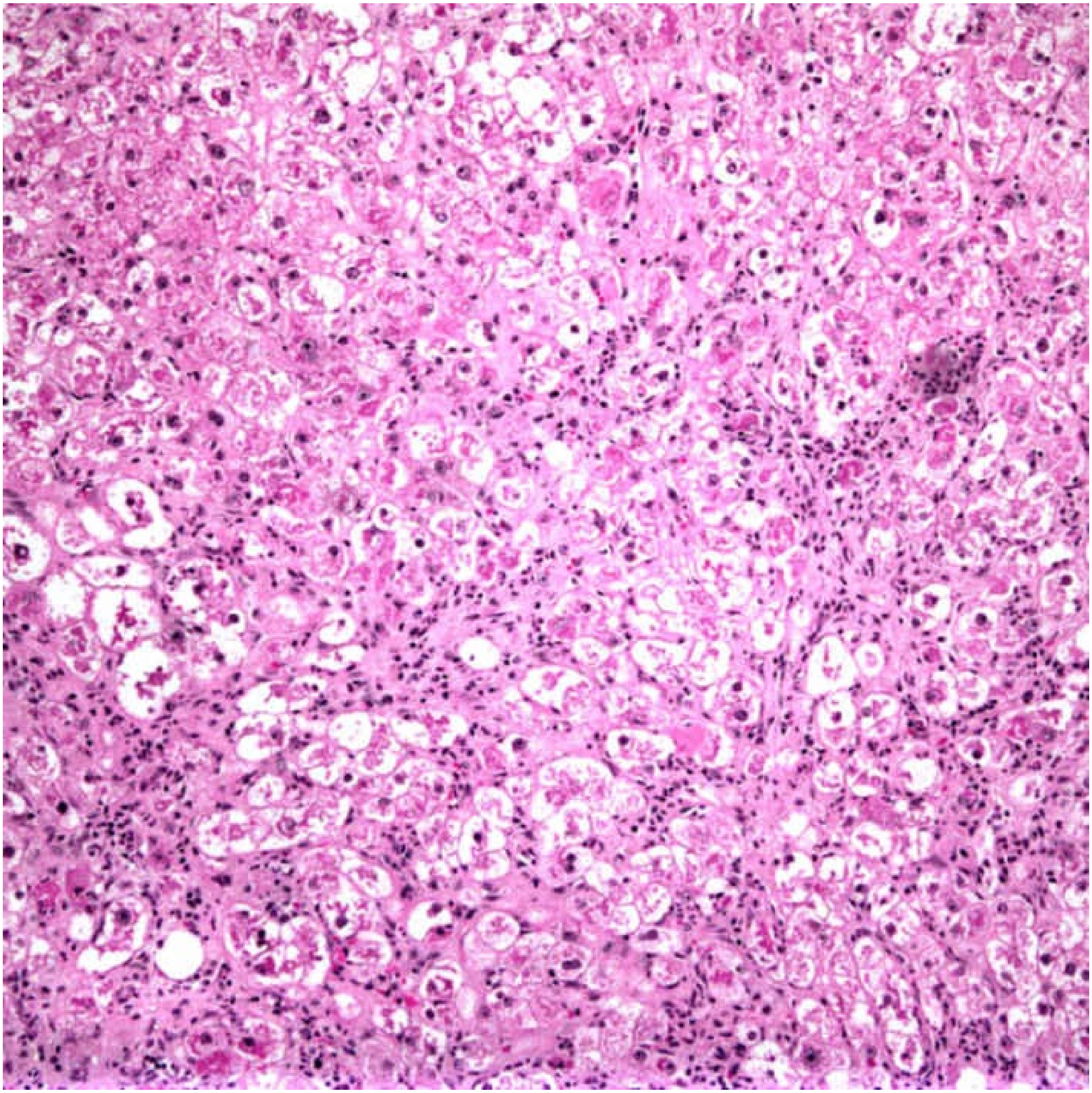
DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

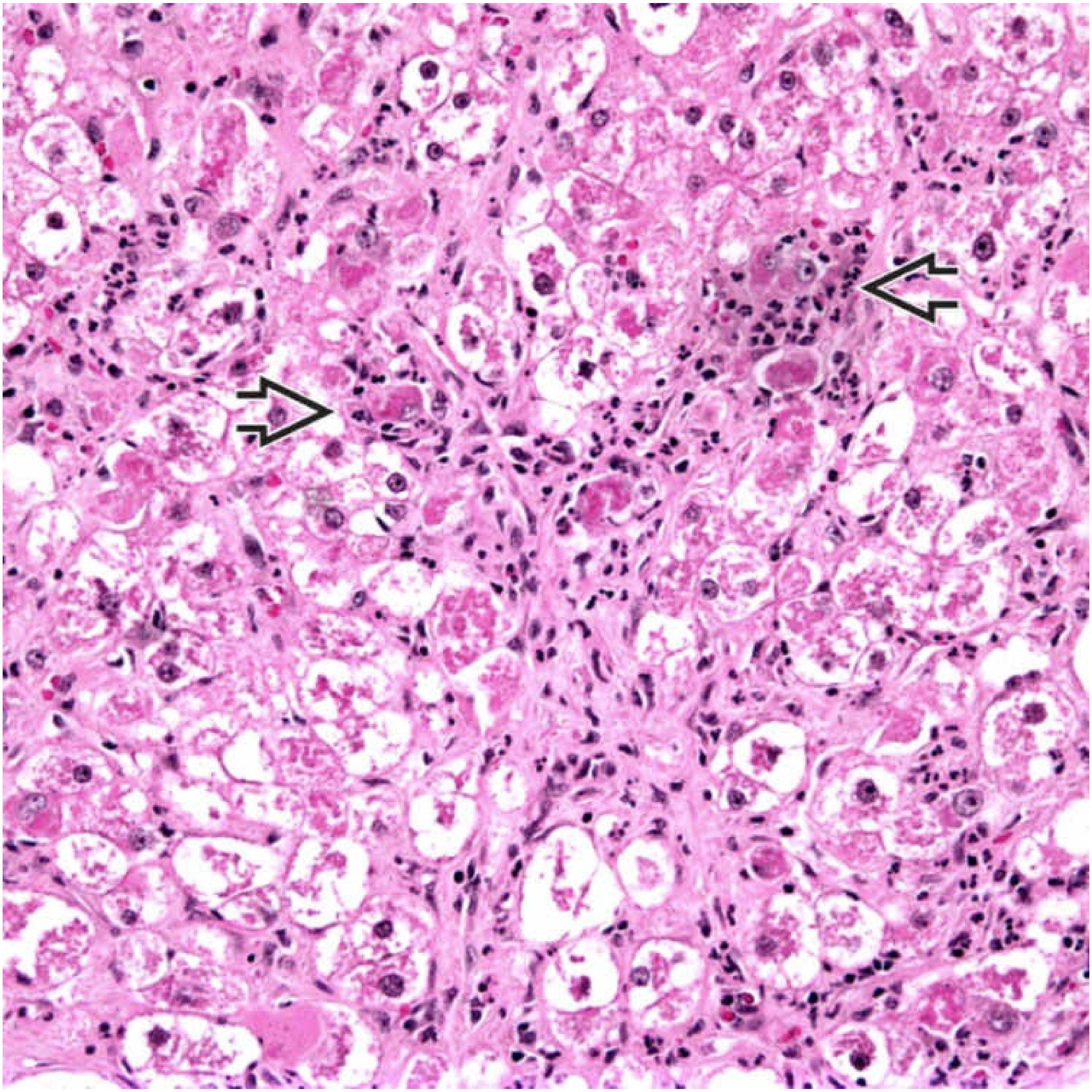
- Appropriate history of exposure to offending drug is necessary for diagnosis



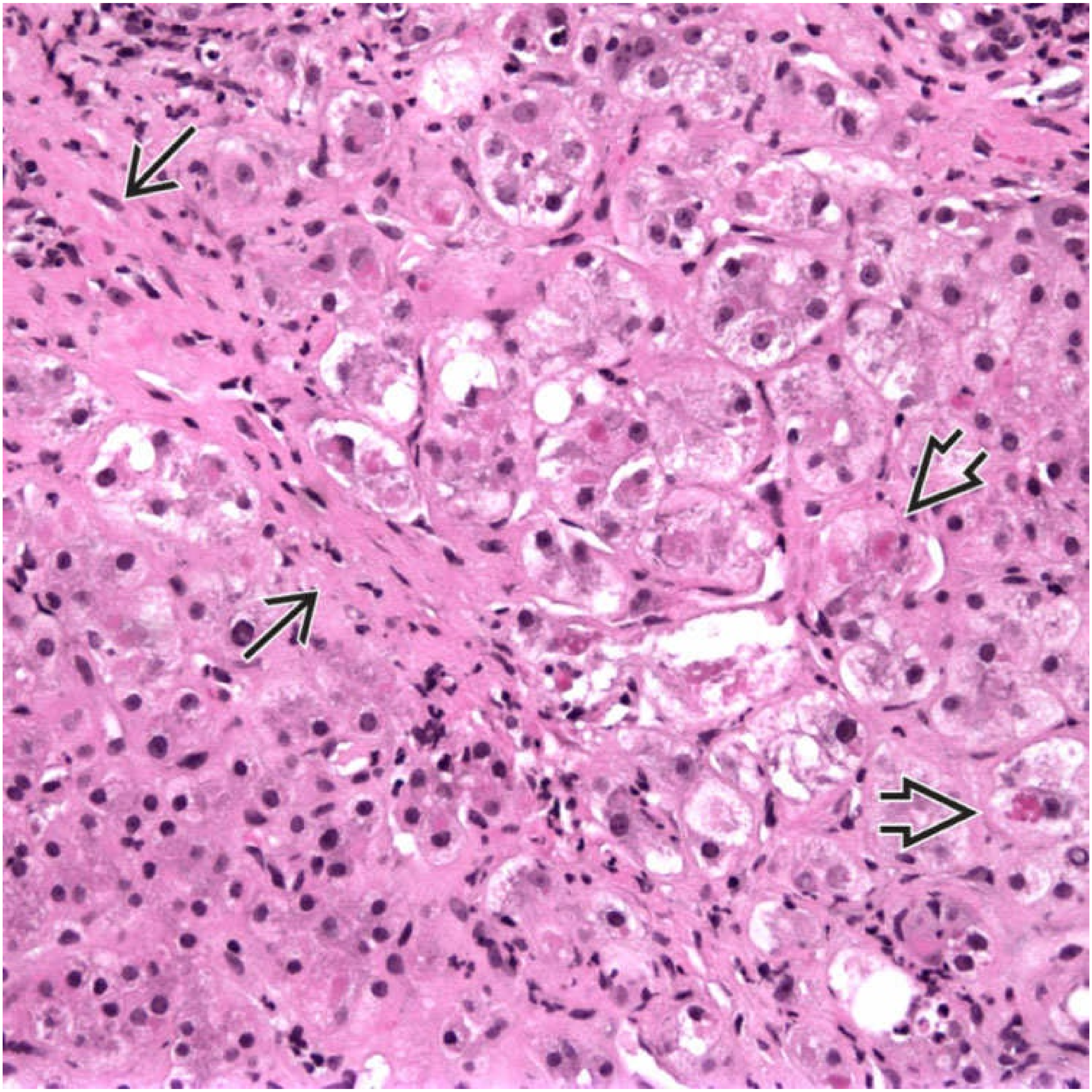
Amiodarone, Steatosis
Fat is not always prominent in amiodarone toxicity, but this case shows abundant microvesicular and macrovesicular fat.



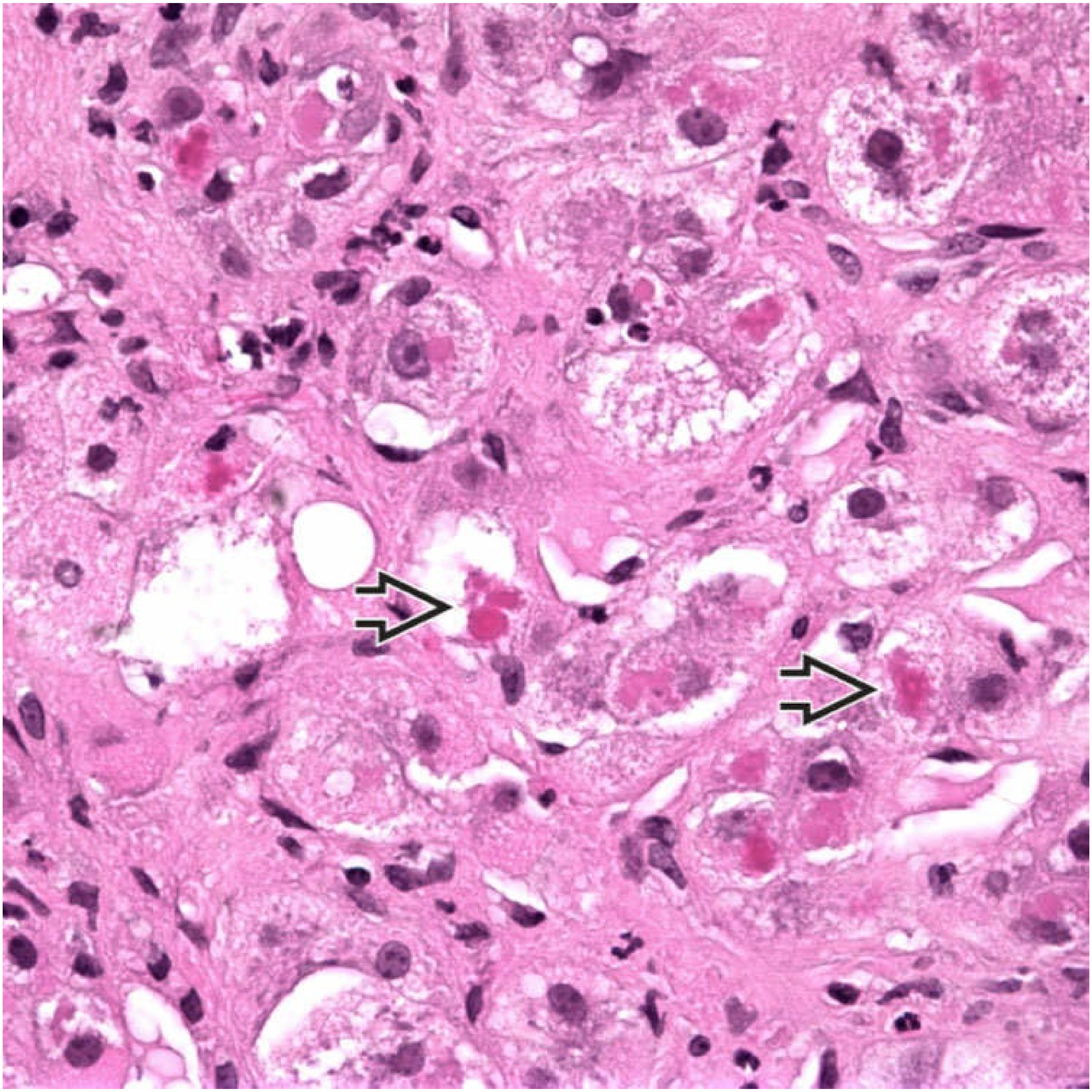
Amiodarone, Ballooned Hepatocytes and Lobular Disarray
Low-power photomicrograph of amiodarone toxicity shows lobular disarray with foamy, ballooned hepatocytes containing Mallory hyaline and a neutrophilic infiltrate.



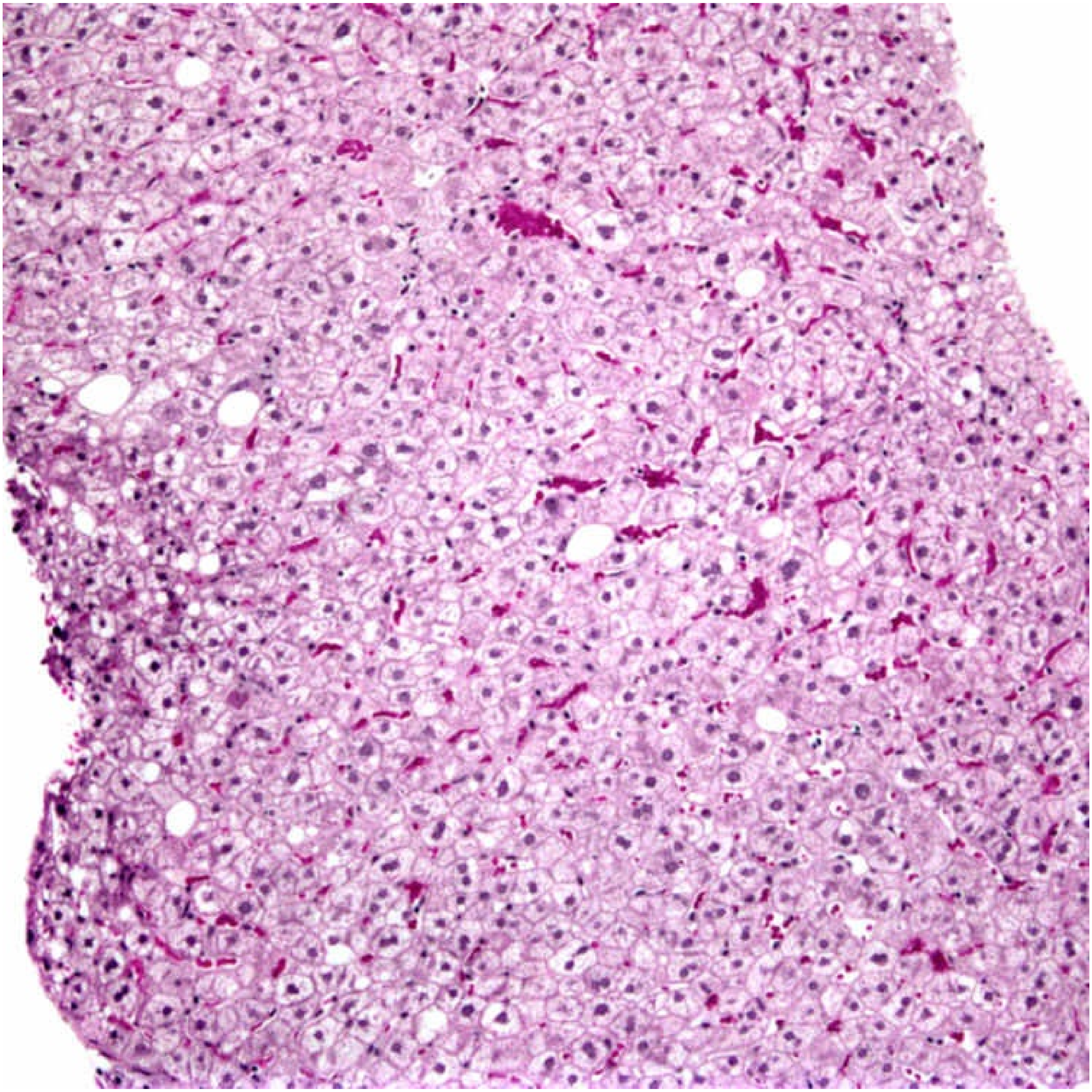
Amiodarone, Neutrophils and Mallory Hyaline
Ballooned hepatocytes containing abundant Mallory hyaline are surrounded by neutrophils, known as satellitosis ⇨. This is a frequent feature of amiodarone toxicity. Steatosis may or may not be present.



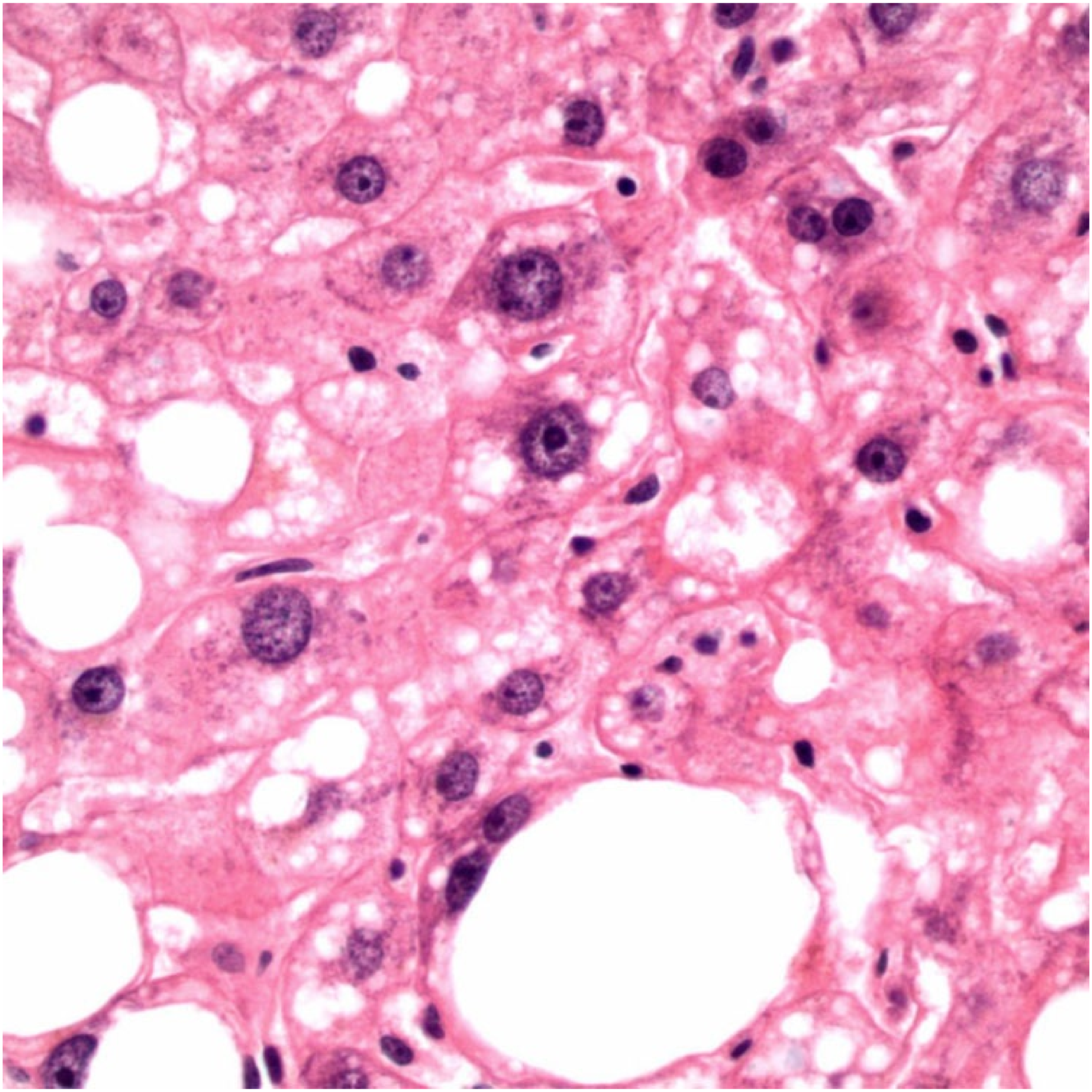
Amiodarone, Mallory Hyaline
Ballooned hepatocytes containing Mallory hyaline ⇨ are visible in this photomicrograph of amiodarone toxicity. Fat and inflammation may not be prominent. Fibrosis is evident → even on H&E.



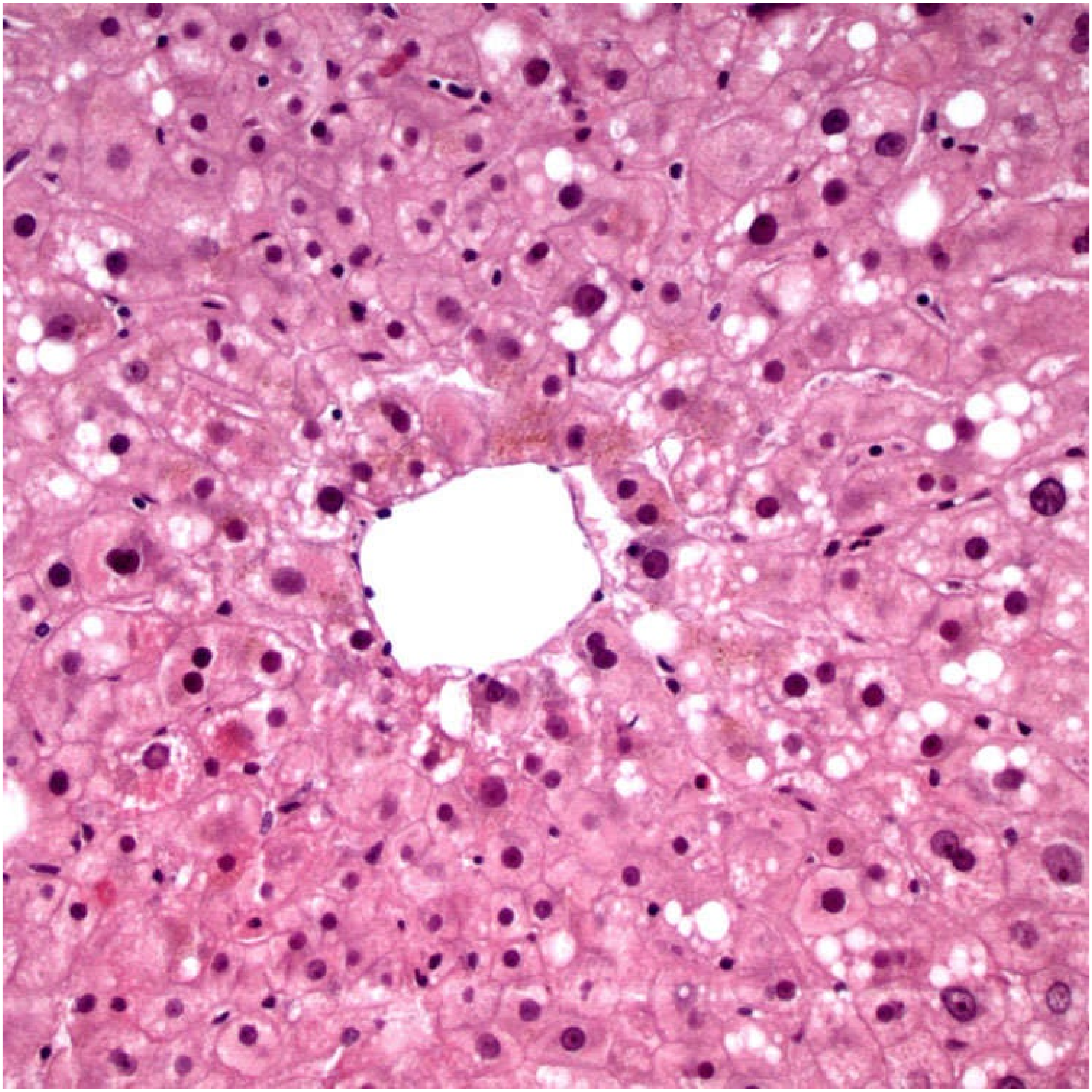
Amiodarone, Hepatocyte Ballooning and Mallory Hyaline
High-power photomicrograph illustrates abundant dark pink, irregular clumps of Mallory hyaline ⇨ within ballooned hepatocytes.



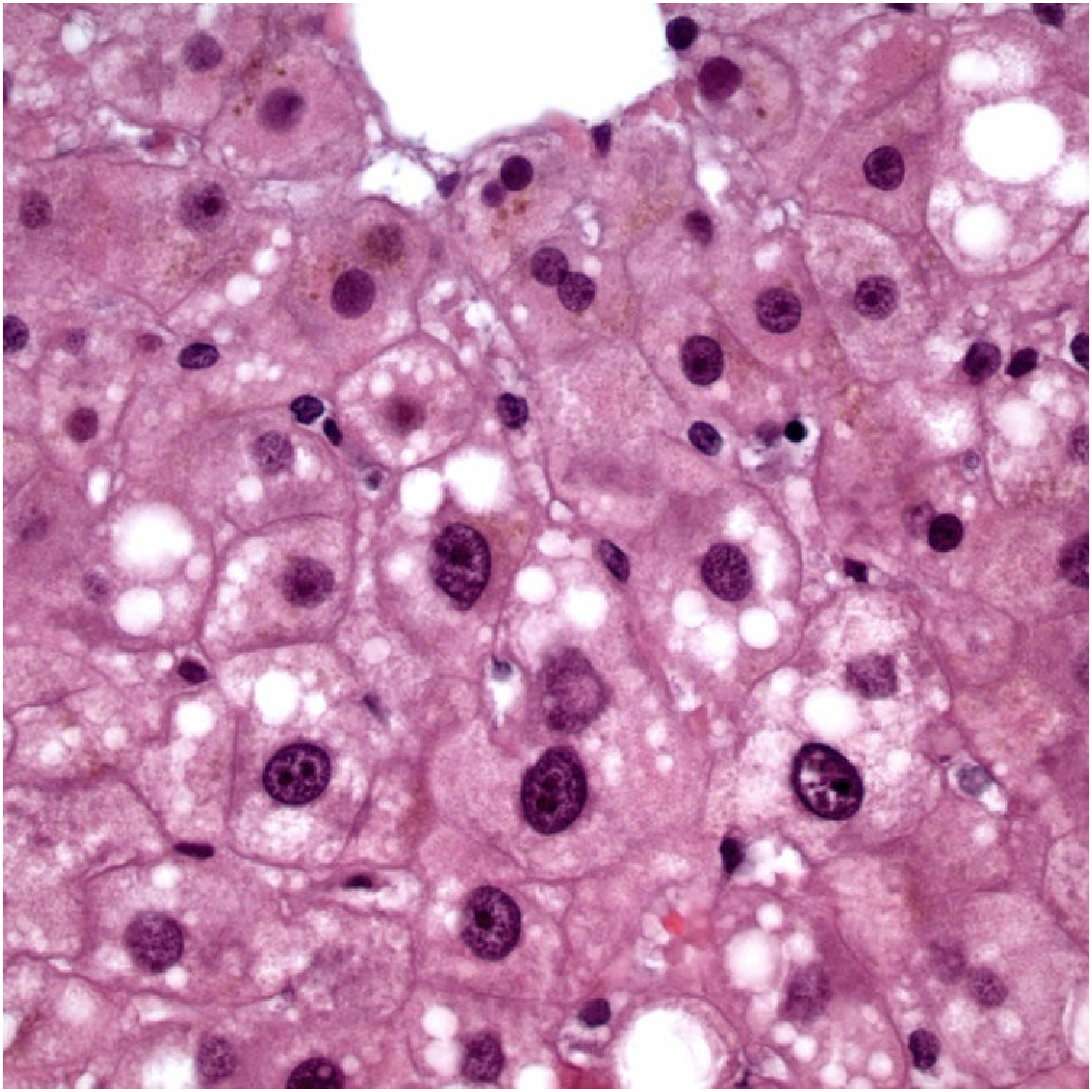
Methotrexate, Mild Reactive Changes and Steatosis
Low-power view of a liver biopsy shows mild methotrexate injury featuring mild macrovesicular steatosis and reactive hepatocellular changes but minimal inflammation.



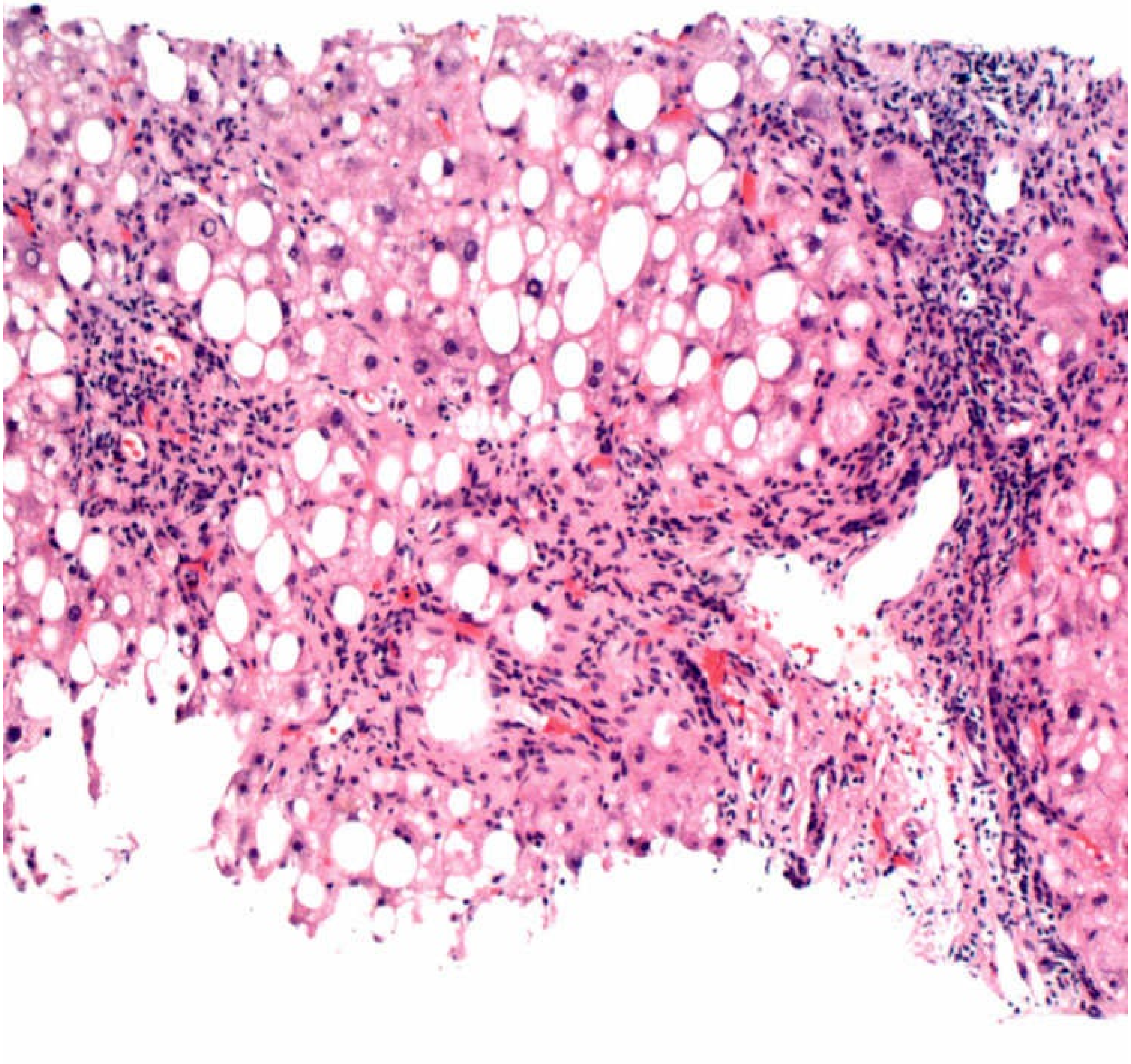
Methotrexate, Steatosis
High-power view of methotrexate injury shows both micro- and macrovesicular steatosis, along with nuclear anisocytosis (variation in nuclear size).



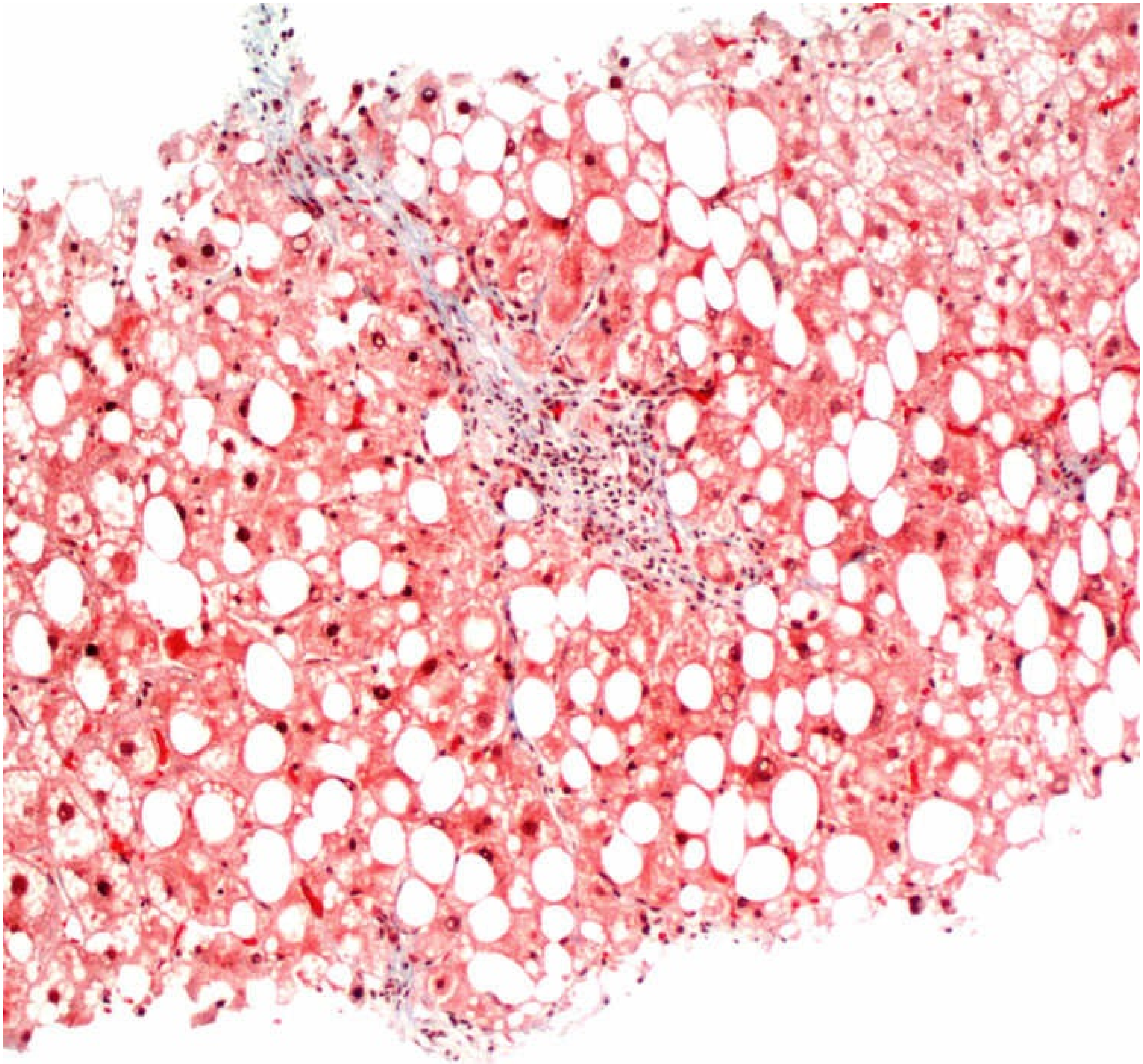
Methotrexate, Reactive Nuclear Anisocytosis
Marked nuclear anisocytosis is a reactive change commonly seen in methotrexate toxicity.



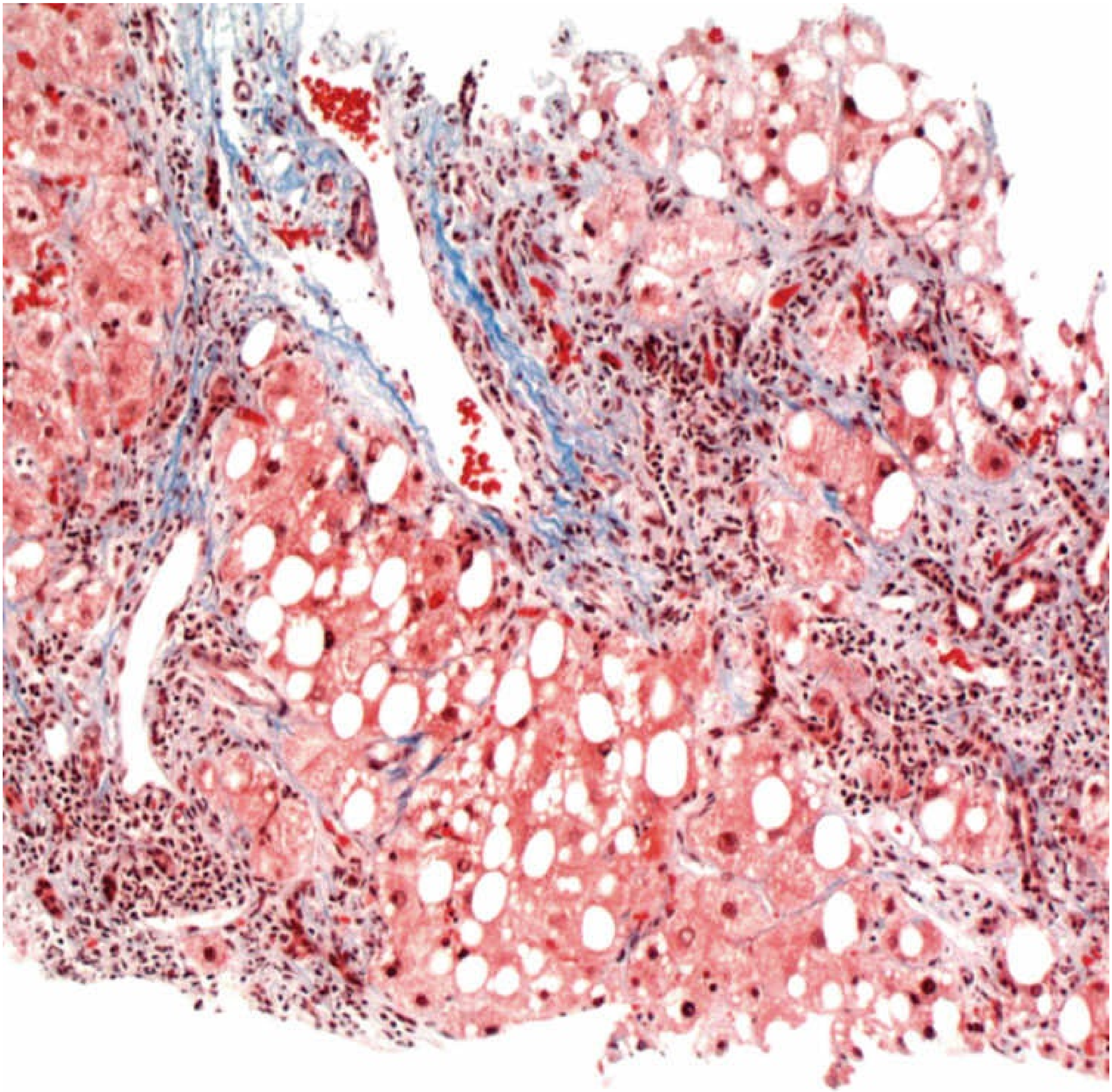
Methotrexate, Reactive Epithelial Changes
Reactive changes commonly seen in methotrexate injury include nuclear anisocytosis and double nuclei in hepatocytes. Steatosis is also present.



Methotrexate, Steatosis and Portal Expansion
Liver biopsy in methotrexate injury shows steatosis, mild portal inflammation, and expansion of portal/periportal areas by fibrosis.



Methotrexate, Periportal Fibrosis and Steatosis
Trichrome stain in methotrexate injury shows steatosis and delicate, irregular spurs of connective tissue extending out from the portal tract.



Methotrexate, Bridging Fibrosis
Trichrome stain illustrates more advanced fibrosis in methotrexate toxicity, consisting of an increase in portal/periportal fibrosis as well as established bridging fibrosis.

SELECTED REFERENCES

1. Loulergue, P, et al. Hepatic steatosis as an emerging cause of cirrhosis in HIV-infected patients. *J Acquir Immune Defic Syndr*. 2007; 45(3):365.
2. Anderson, N, et al. Drug-induced phospholipidosis. *FEBS Lett*. 2006; 580(23):5533–5540.
3. Grismer, LE, et al. Liver biopsy in psoriatic arthritis to detect methotrexate hepatotoxicity. *J Clin Rheumatol*. 2001; 7(4):224–227.
4. Lewis, JH, et al. Histopathologic analysis of suspected amiodarone hepatotoxicity. *Hum Pathol*. 1990; 21(1):59–67.

5.Kremer, JM, et al. Liver histology in rheumatoid arthritis patients receiving long-term methotrexate therapy. A prospective study with baseline and sequential biopsy samples. *Arthritis Rheum*. 1989; 32(2):121–127.

6.Lewis, JH, et al. Amiodarone hepatotoxicity: prevalence and clinicopathologic correlations among 104 patients. *Hepatology*. 1989; 9(5):679–685.
7.Roenigk, HH, Jr., et al. Methotrexate in psoriasis: revised guidelines. *J Am Acad Dermatol*. 1988; 19(1 Pt 1):145–156.
8.Nyfors, A, et al. Morphogenesis of fibrosis and cirrhosis in methotrexate-treated patients with psoriasis. *Am J Surg Pathol*. 1977; 1(3):235–243.

Reye Syndrome

KEY FACTS

Terminology

- Acute and potentially life-threatening disorder characterized by fatty liver and encephalopathy
  - Most often seen in children
  - Classic syndrome involves combination of resolving viral illness and salicylate therapy

Etiology/Pathogenesis

- Pathogenesis unknown
- Mitochondrial injury is a key feature
- Frequent antecedent viral infection
- Salicylate exposure appears to play role although no causal connection proven

Clinical Issues

- Clinical picture dominated by neurologic rather than hepatic manifestations
  - Clinical evidence of hepatic disease may be very subtle
- Biphasic pattern: Viral prodrome followed by neurologic manifestations
  - Prodromal febrile illness
  - Vomiting and neurologic alterations 3-5 days later
- Mortality ~ 30%
  - Death usually due to cerebral edema and complications

Microscopic

- Diffuse, panlobular microvesicular steatosis
- No significant inflammation

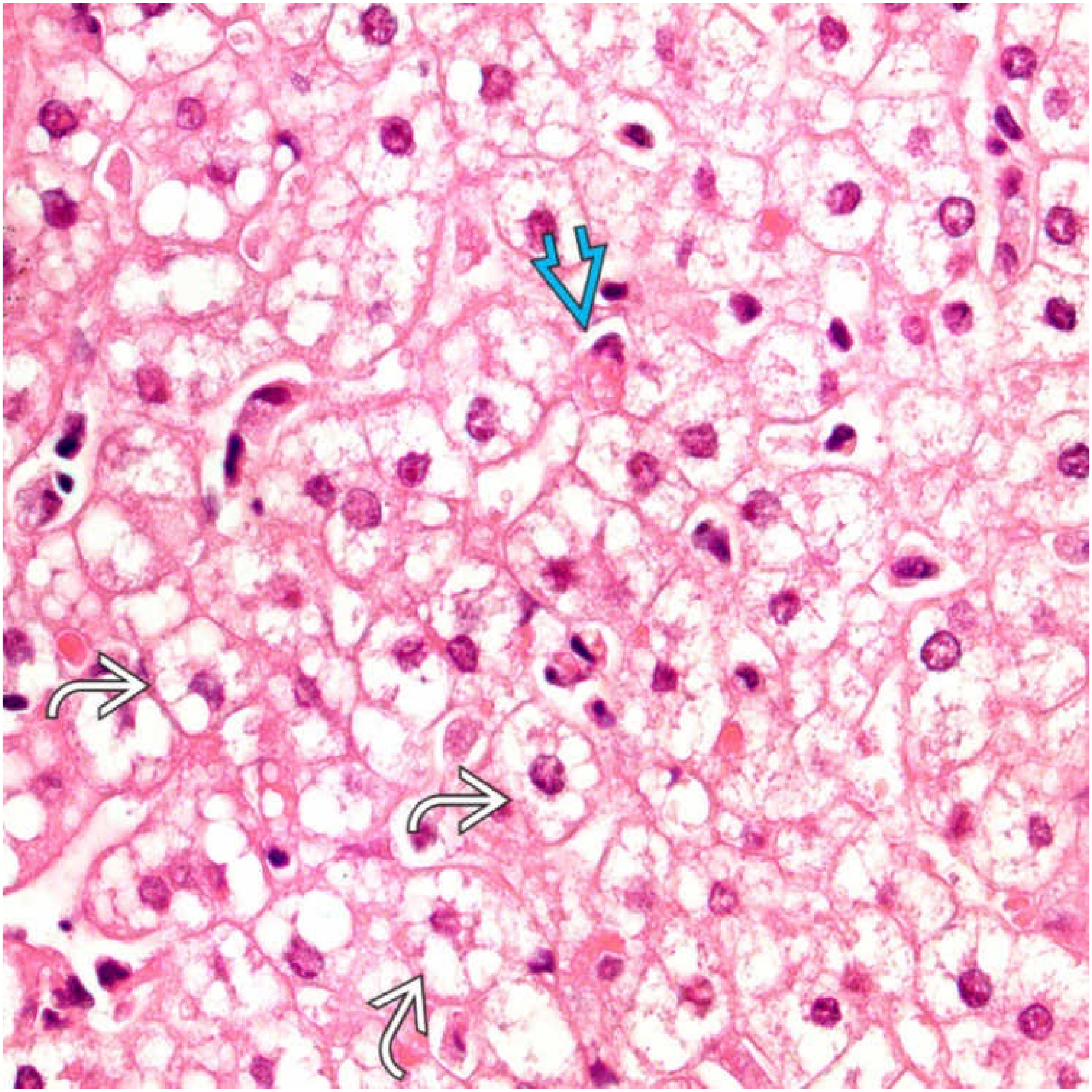
Top Differential Diagnoses

- Congenital metabolic conditions

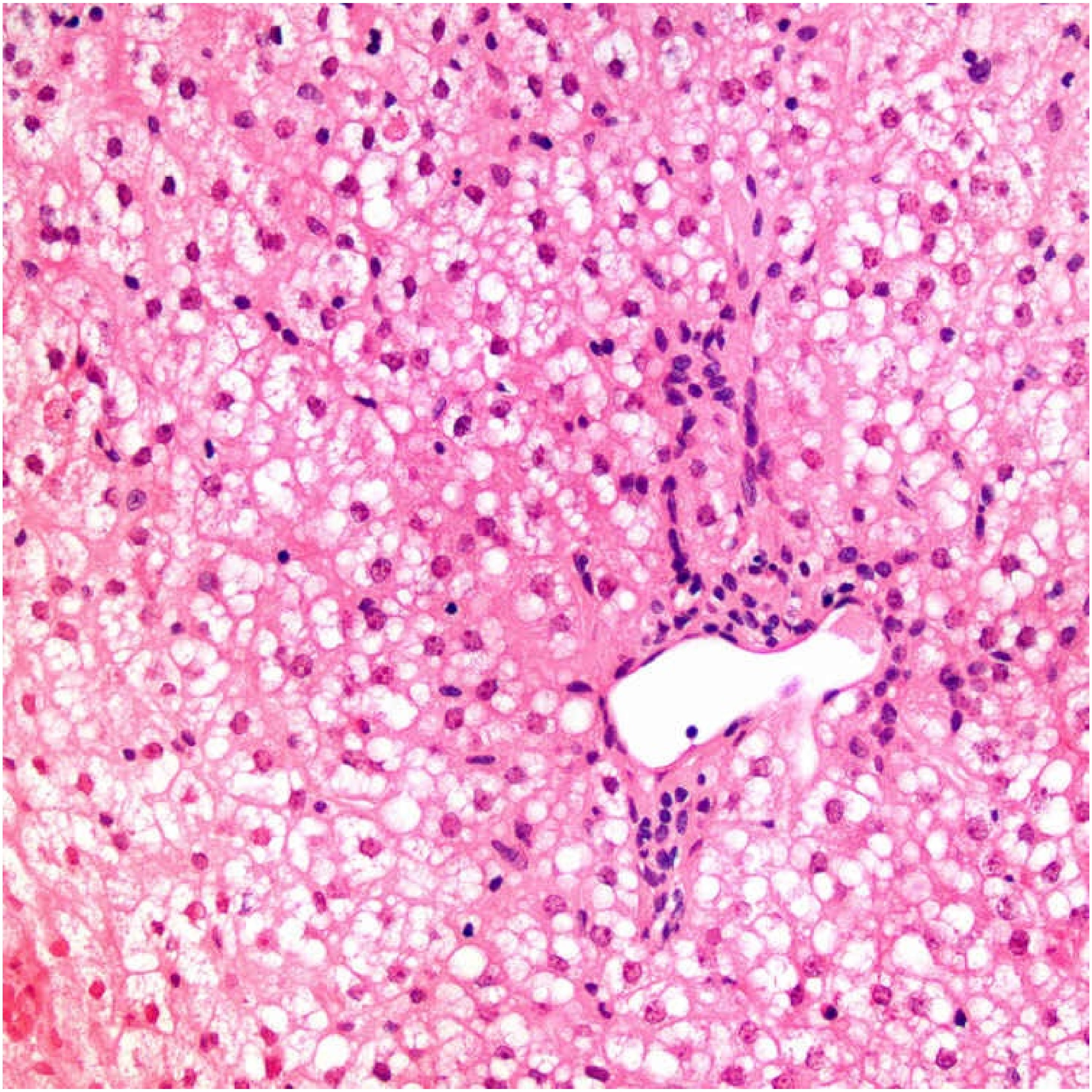
- Acute fatty liver of pregnancy
- Alcoholic foamy degeneration
- Drug/toxin-mediated injury
- Sepsis

Diagnostic Checklist

- Presumptive diagnosis can be made based on clinical and laboratory findings
- Microvesicular fatty change in context of neurologic alterations/encephalopathy
- Necessity of liver biopsy for diagnosis is controversial

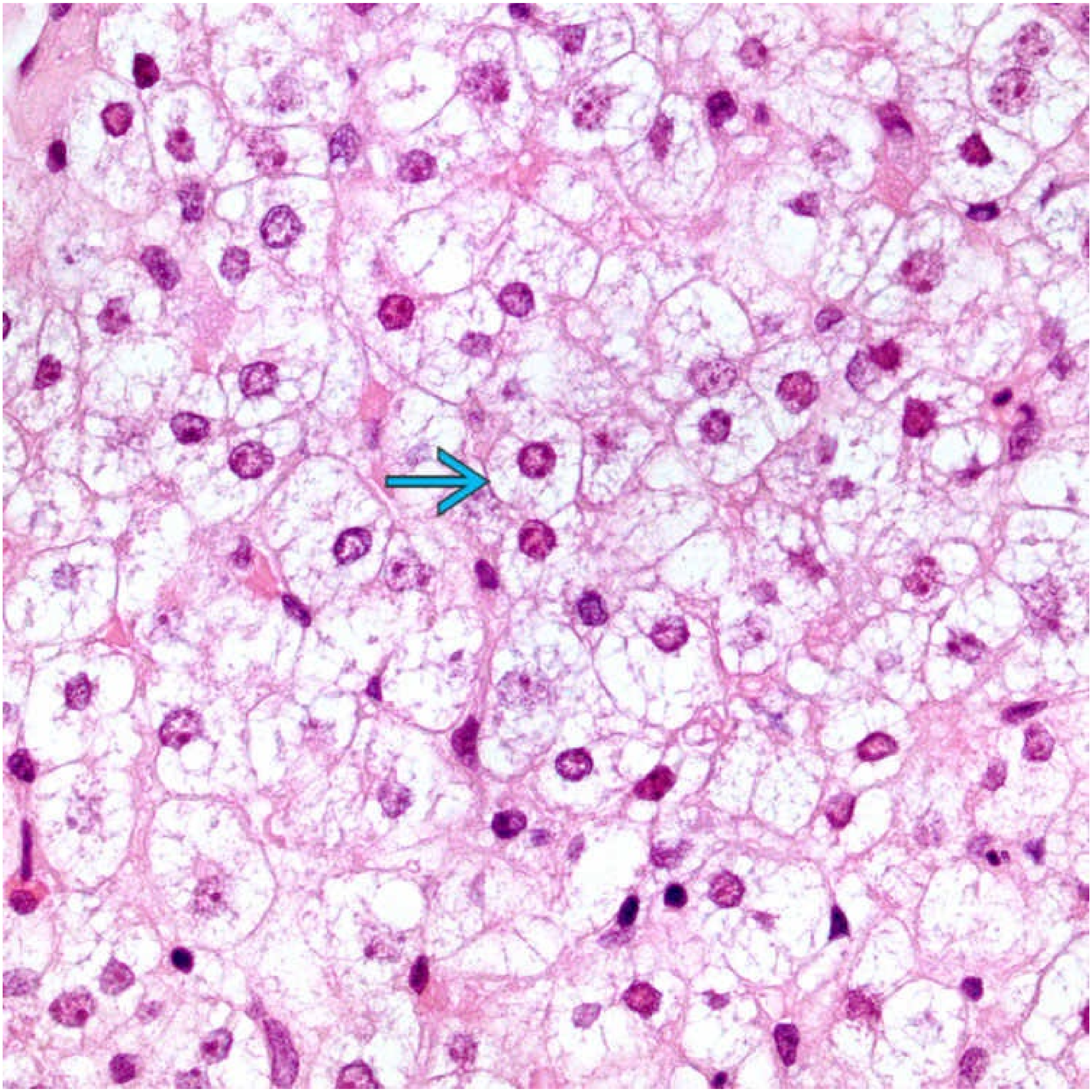


Microvesicular Steatosis
Diffuse microvesicular steatosis and occasional acidophil bodies are seen in a case of Reye syndrome. Cholestasis is rare in this disorder.



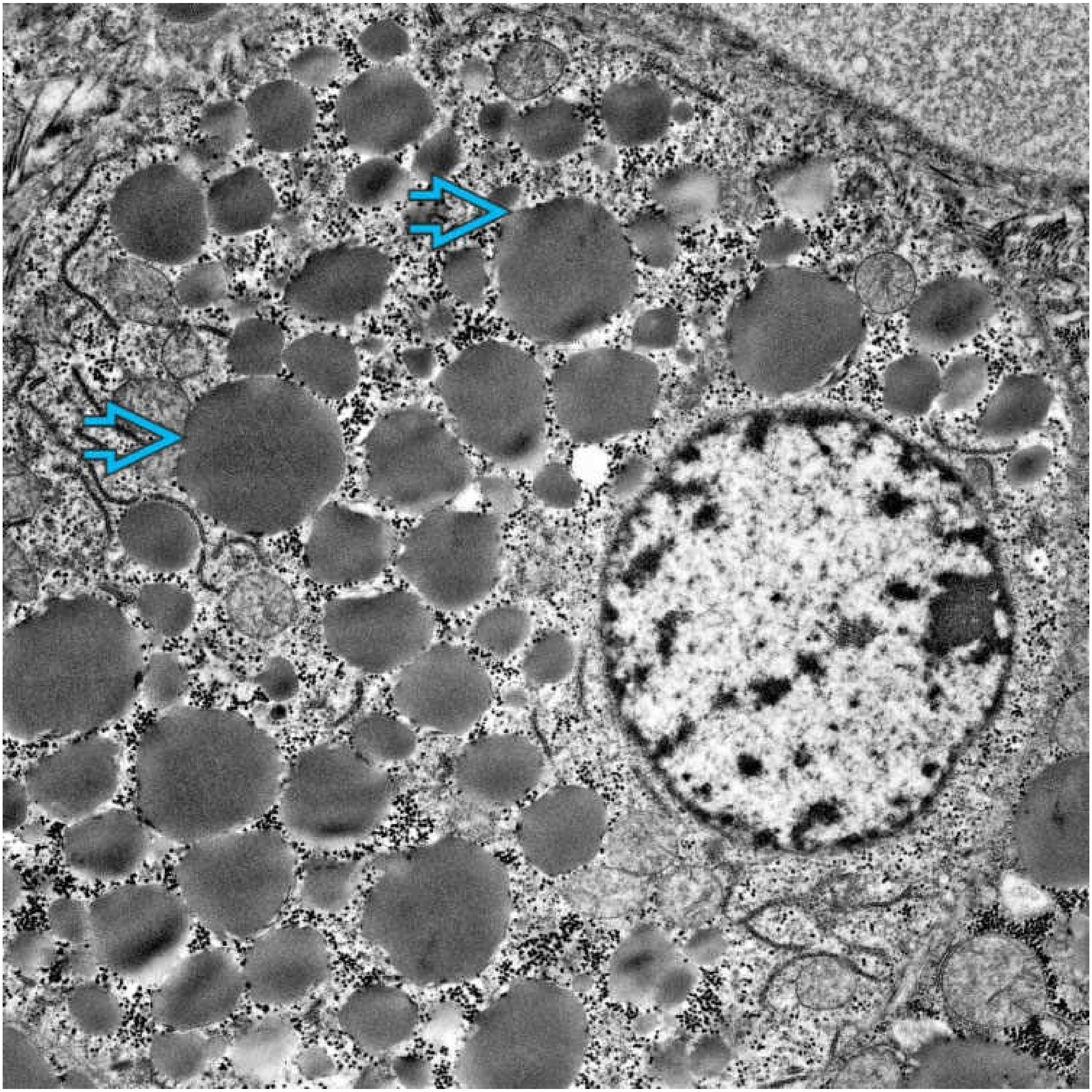
Absence of Portal Inflammation

An intact portal tract with no portal inflammation is seen in a biopsy from a patient with Reye syndrome. Portal inflammation is typically absent. Diffuse background microvesicular steatosis is also seen.



Microvesicular Steatosis

Microvesicular steatosis is characteristic of Reye syndrome. Numerous tiny fat vacuoles surround the hepatocyte nucleus →, which retains its central location within the hepatocyte. This change can be subtle and may be mistaken for hepatocyte swelling or an artifact.



Microvesicular Steatosis on Electron Microscopy
This electron micrograph shows numerous lipid droplets within a hepatocyte in a patient with Reye syndrome. (Courtesy E. Sengupta, MD.)

TERMINOLOGY

Definitions

- Acute and potentially life-threatening disorder characterized by fatty liver and encephalopathy
    - Most common in infants and children under 17 years
    - Worldwide distribution
- "Classic" or "idiopathic" syndrome: Combination of resolving flu-like illness and salicylate therapy
- Reye-like syndrome: Patients presumed to have metabolic disorder unless clear evidence of viral

illness and salicylate use
  - Many children with acute Reye syndrome-like illness diagnosed with metabolic disorder such as mitochondrial fatty acid oxidation defect

ETIOLOGY/PATHOGENESIS

Pathogenesis Unknown

- Mitochondrial injury is fundamental feature
  - Failure of mitochondrial function results in carbohydrate, amino acid, and fatty acid metabolic derangement
- Initiating factors remain obscure
  - Frequent antecedent viral infection
  - Salicylate exposure appears to play role although no causal connection has been proven
    - Reye syndrome has decreased as pediatric salicylate exposure has decreased

CLINICAL ISSUES

Presentation

- Biphasic pattern
  - Prodromal febrile illness, often influenza B or varicella
  - Vomiting and neurologic alterations 3-5 days later
  - Lethargy and irritability initially; can progress to delirium, obtundation, seizures, coma
- Clinical evidence of liver disease often absent
- Jaundice absent
- Metabolic acidosis, respiratory alkalosis can be present

Laboratory Tests

- CSF has normal glucose and protein; minimal leukocytosis
  - Increased transaminases, often marked
  - Increased serum ammonia
  - Normal bilirubin
  - Electron microscopy
  - Enlarged, swollen, pleomorphic mitochondria with disrupted, fragmented cristae
  - Lucent matrix and loss of matrical dense bodies
  - Mitochondria may decrease in number as disease progresses

Treatment

- Supportive care
- Controlling increased intracranial pressure
- Correcting metabolic abnormalities

Prognosis

- Dominated by neurologic rather than hepatic manifestations
  - Death usually due to cerebral edema and complications
- Mortality ~ 30%
  - Those who survive acute illness usually recover completely
  - Small percentage have long-term neurologic sequelae
  - Diagnosis before irreversible brain damage occurs is critical

MACROSCOPIC

General Features

- Mild hepatomegaly with yellow discoloration

MICROSCOPIC

Histologic Features

- Diffuse, panlobular microvesicular steatosis
  - Most evident during 1st 3-4 days of illness
  - Droplets may be so small as to be missed
  - Lipid can be demonstrated using oil red O or Sudan black B stains in frozen sections
- Minimal or absent inflammation
- Enlarged, central hepatocyte nuclei
- Depleted glycogen
- Necrosis, cholestasis rare

DIFFERENTIAL DIAGNOSIS

Acute Fatty Liver of Pregnancy

- Different clinical scenario

Alcoholic Foamy Degeneration

- Associated with ethanol use
- Elevated bilirubin
- Other changes of alcoholic liver disease often present

Drug/Toxin-Mediated Injury

- Valproic acid, IV tetracycline, salicylates

Congenital Metabolic Conditions

- Urea cycle disorders, fatty acid metabolism defects, lysosomal lipase deficiency

- Electron microscopy and extensive metabolic work-up may be needed to distinguish from Reye syndrome

Sepsis

- e.g., toxic shock syndrome

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Presumptive diagnosis can be made based on clinical and laboratory findings
  - Necessity of liver biopsy for diagnosis is controversial

Pathologic Interpretation Pearls

- Microvesicular fatty change in context of neurologic alterations/encephalopathy

SELECTED REFERENCES

1. Gosalakkal, JA, et al. Reye syndrome and reye-like syndrome. *Pediatr Neurol*. 2008; 39(3):198–200.
2. Saudubray, JM, et al. Recognition and management of fatty acid oxidation defects: a series of 107 patients. *J Inherit Metab Dis*. 1999; 22(4):488–502.
3. Stanley, CA, et al. Genetic disorders of mitochondrial fatty acid oxidation. *Curr Opin Pediatr*. 1994; 6(4):476–481.
4. Crocker, JF. Reye's syndrome. *Semin Liver Dis*. 1982; 2(4):340–352.
5. Starko, KM, et al. Reye's syndrome and salicylate use. *Pediatrics*. 1980; 66(6):859–864.
6. Reye, RD, et al. Encephalopathy and fatty degeneration of the viscera. A disease entity in childhood. *Lancet*. 1963; 2(7311):749–752.

Drug-Related Cholangitis/Ductopenia

KEY FACTS

Terminology

- Bile duct injury, cholangitis, &/or ductopenia related to adverse drug reactions
  - Often accompanied by cholestasis
- Vanishing bile duct syndrome
  - Used to describe ductopenia related to drugs but not specific term

Etiology/Pathogenesis

- Many medication classes implicated
  - Antiinflammatory, antibiotics, antiepileptics, psychiatric drugs, tranquilizers, hypoglycemics, and others
- Also occurs with herbal or toxin exposure or genetic disposition

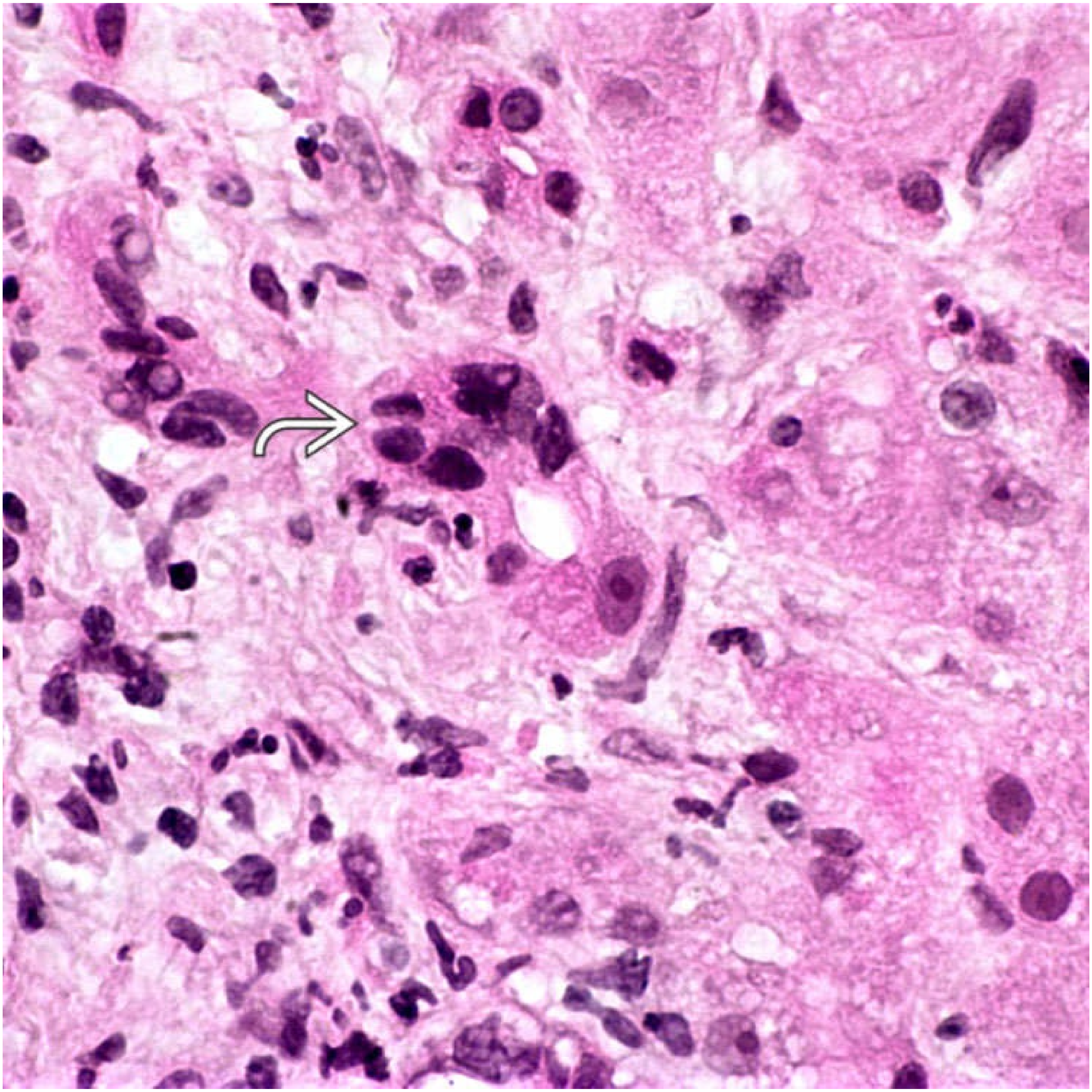
Clinical Issues

- Jaundice
  - Temporal relationship between drug administration and onset of signs and symptoms
  - Most patients recover fully with discontinuation of drug
  - Few cases develop chronic cholestatic injury

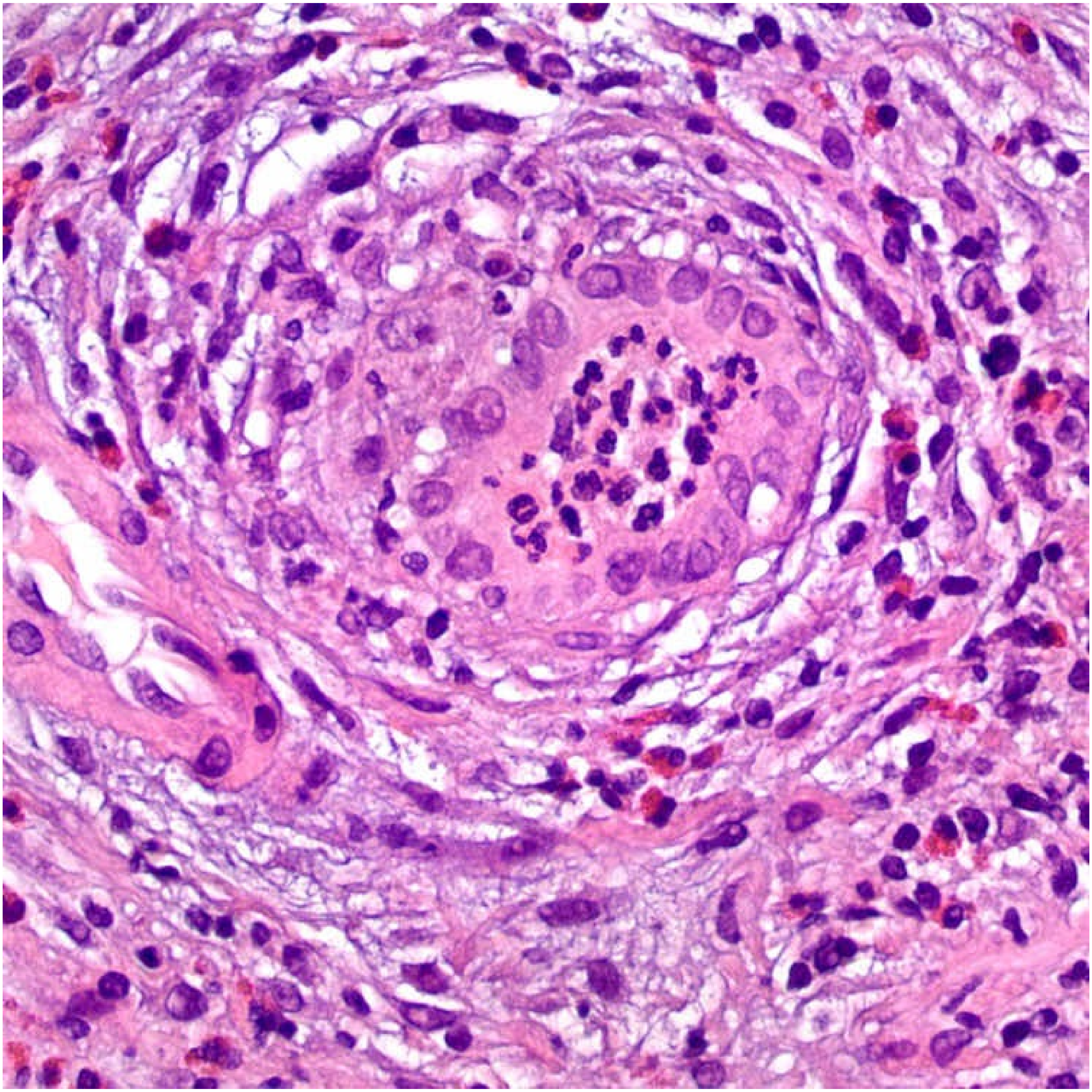
Microscopic

- Generally, no specific features indicating injury is drug related
  - Cholestasis, usually zone 3
  - Bile duct epithelial cell injury
    - Cytoplasmic eosinophilia &/or vacuolization
    - Nuclear pleomorphism and uneven nuclear spacing
    - Apoptosis and atrophy of ductal epithelium
  - Bile ductular proliferation
  - Lymphocytic or mixed cell cholangitis

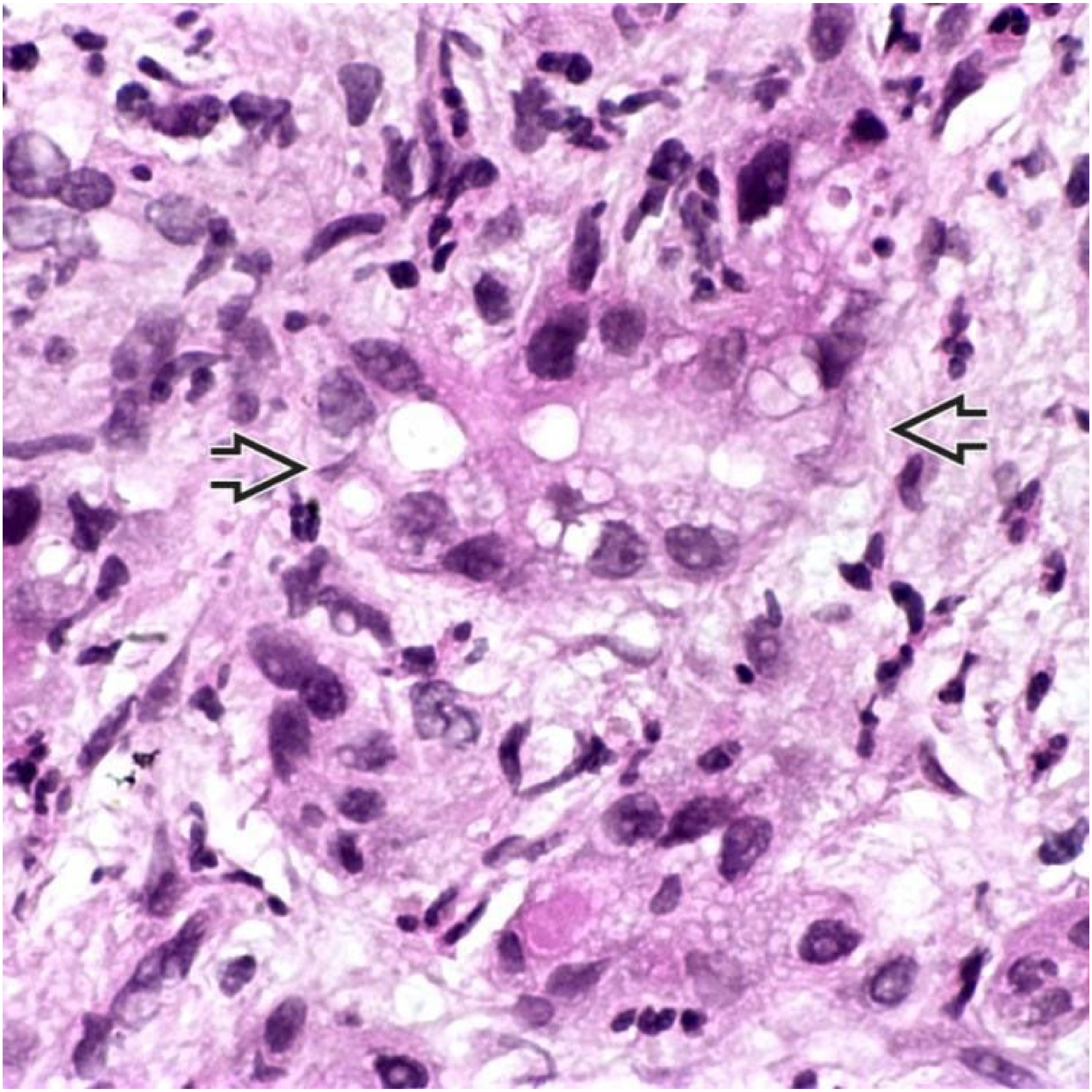
- Some cases show changes of progression/chronicity
  - Progressive ductopenia
  - Periportal hepatocyte swelling and copper accumulation



Bile Duct Injury Secondary to ACE Inhibitor
This example of drug-induced cholangitis due to an ACE inhibitor shows a damaged duct with eosinophilic cytoplasm, irregular spaces between nuclei, and variation in nuclear size and shape.

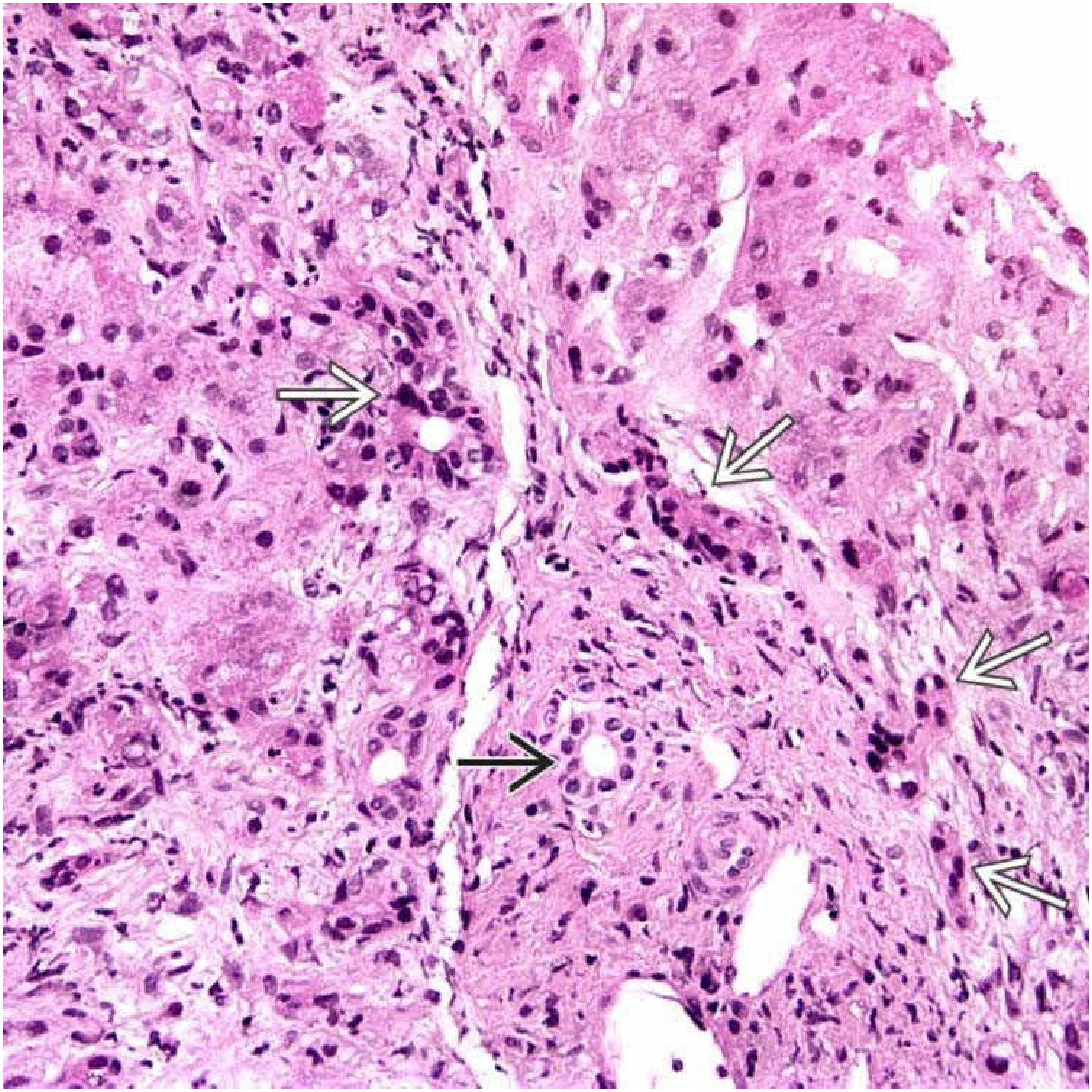


Cholangitis With Neutrophils and Eosinophils
This example of drug-related cholangitis due to antibiotics shows a duct with cholangitis surrounded by portal edema and an infiltrate that is rich in eosinophils.



Drug-Related Bile Duct Injury

This severely injured duct ⇨ shows marked cytoplasmic vacuolization and eosinophilia as well as irregularly spaced nuclei.



Ductular Reaction
Numerous proliferating bile duct profiles ⇒ are seen at the edge of this portal tract in a case of drug-related cholangitis. The native bile duct is distinct → from these proliferating bile duct profiles.

TERMINOLOGY

Synonyms

- Cholangiodestructive cholestasis
  - Vanishing bile duct syndrome: Ductopenia related to drugs but not specific entity, ductopenia in graft-vs.-host disease and chronic ductopenic rejection
  - Stevens-Johnson syndrome
    - Drug reaction associated with severe mucocutaneous manifestations and vanishing bile duct syndrome

Definitions

- Bile duct injury, cholangitis, &/or ductopenia related to adverse drug reactions
  - Often accompanied by cholestasis

ETIOLOGY/PATHOGENESIS

2 Categories of Injury

- Predictable: Dose related, reproducible, and related to intrinsic toxicity of drug or its metabolites
  - Idiosyncratic: Unpredictable, unrelated to dose, not reproducible in animal models
  - Allergic or autoimmune responses to drug or its metabolite may be involved

Drugs

- Many medication classes implicated
  - Antiinflammatory: Acetaminophen, ibuprofen, phenylbutazone
  - Antibiotics: Amoxicillin-clavulanic acid, ampicillin, clindamycin, erythromycin, tetracycline, trimethoprim/sulfamethoxazole
  - Antiepileptics: Carbamazepine, phenytoin
  - Psychiatric drugs: Amitriptyline, imipramine, Haldol
  - Tranquilizers: Chlorpromazine, prochlorperazine, phenothiazine
  - Hypoglycemics: Tolbutamide, chlorpropamide
  - Other: Cromolyn sodium (antiasthmatic), cyproheptadine (antihistamine), methyltestosterone, thiabendazole (antihelminthic)

Herbal Preparations

- May not be reported by patients as part of medication and exposure history

Toxins

- Paraquat, rapeseed oil

Genetic Predisposition

- Mutations in MDR3 (phospholipid export pump involved in bile secretion) predispose to drug-related cholangitis

CLINICAL ISSUES

Presentation

- Jaundice
  - Temporal relationship between drug administration and onset of signs and symptoms
  - Usually presents within weeks of taking drug but may be delayed up to 1 year

Natural History

- Initial bile duct injury may be followed by ductopenia and prolonged cholestasis
- Effects may persist for months
- May see reduced bile duct numbers on biopsy after clinical recovery

Treatment

- Discontinue offending drug
- Ursodeoxycholic acid may improve cholestasis in some

Prognosis

- Most patients recover fully with discontinuation of drug
  - Few cases develop chronic cholestatic injury
  - Vanishing bile duct syndrome
  - Biliary cirrhosis or sclerosing cholangitis-like picture

MICROSCOPIC

Histologic Features

- **Generally, no specific features indicating injury is drug related**
  - Cholestasis, usually zone 3
  - Bile duct epithelial cell injury
  - Cytoplasmic eosinophilia &/or vacuolization
  - Nuclear pleomorphism and uneven spacing of nuclei
  - Apoptosis and flattening or atrophy of ductal epithelium
- Lymphocytic or mixed cell cholangitis
- Mild to moderate portal inflammation may include large numbers of eosinophils &/or neutrophils
  - Portal edema may be present
- Variable hepatocyte damage and lobular inflammation
- Bile ductular proliferation
- Changes of progression/chronicity
  - Progressive ductopenia: Hepatic artery branches or portal tracts lacking companion bile ducts
    - Diagnosis established by 50% reduction in bile ducts
  - Periportal hepatocyte swelling and copper accumulation
  - Fibrosis
- Vanishing bile duct syndrome
  - Duct loss and cholangiolar proliferation
  - Chronic cholestasis
  - Portal inflammation and fibrosis

DIFFERENTIAL DIAGNOSIS

Primary Biliary Cholangitis

- Positive AMA

Sclerosing Cholangitis

- Primary sclerosing cholangitis: Characteristic ERCP findings, history of inflammatory bowel disease
- Secondary sclerosing cholangitis: Operative trauma, ischemia, cystic fibrosis

Graft-vs.-Host Disease

- Clinical context of transplantation

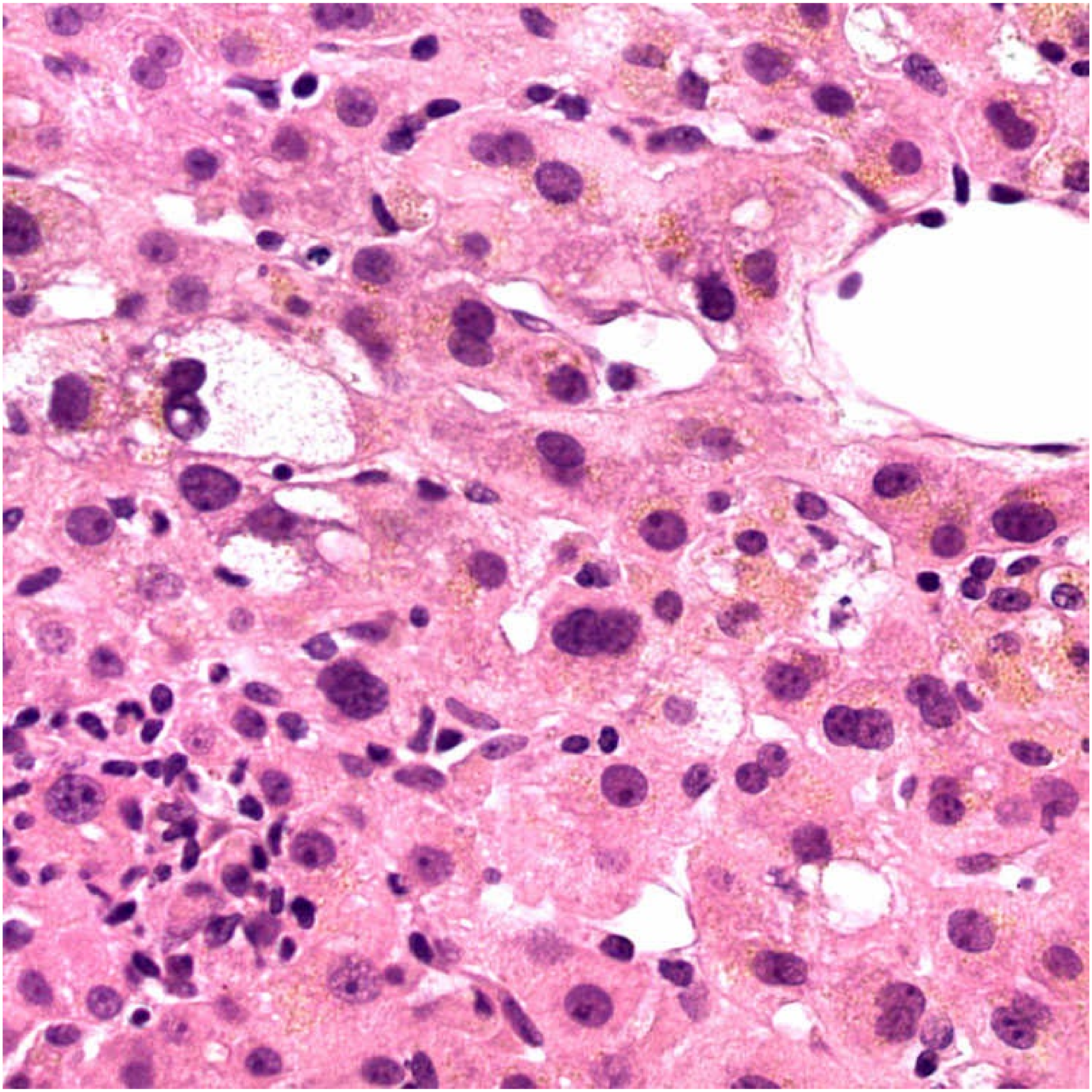
Allograft Rejection

- Clinical context of liver transplantation, presence of endothelialitis

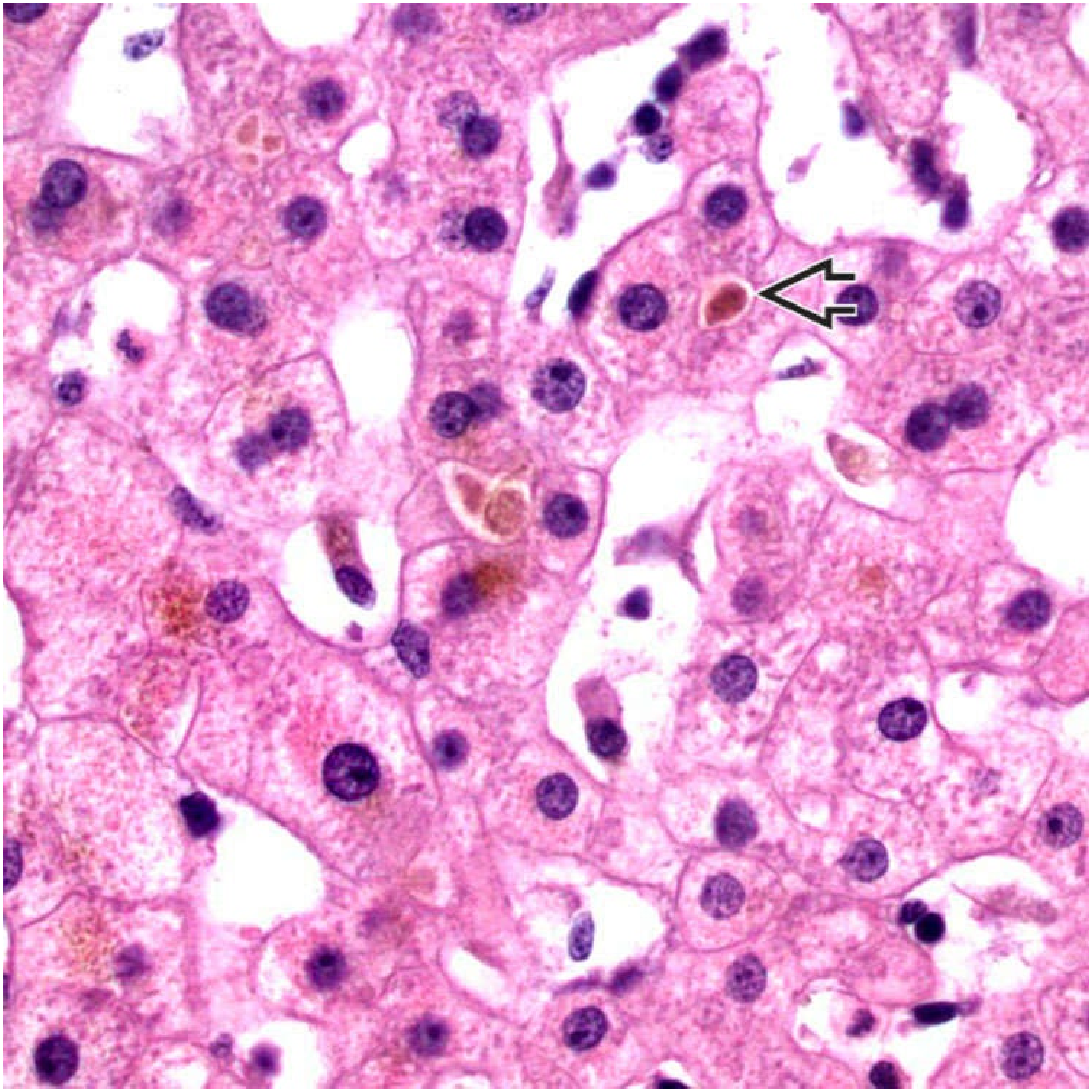
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

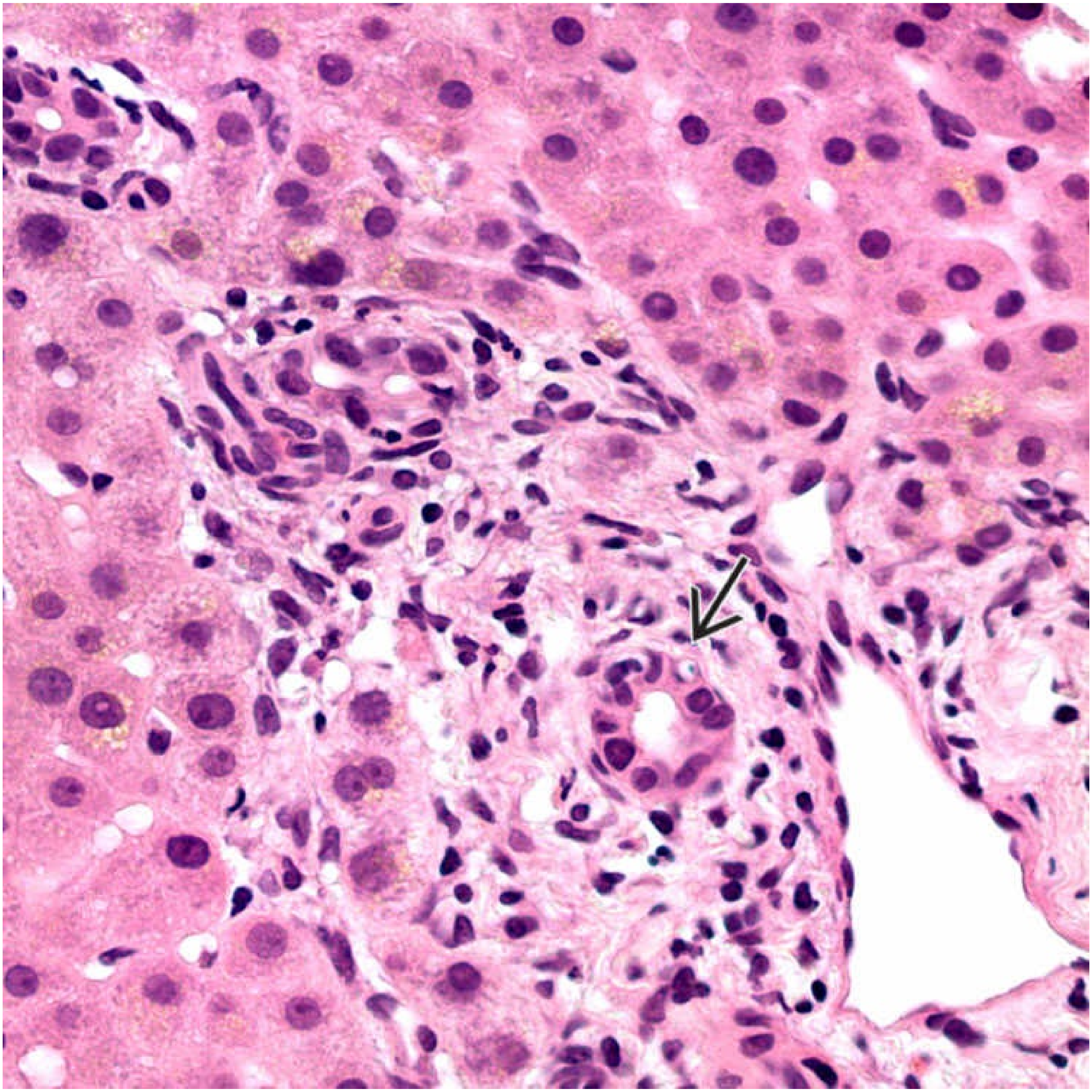
- Histologic features usually cannot provide definite diagnosis of drug-related injury but can assist in excluding other etiologies



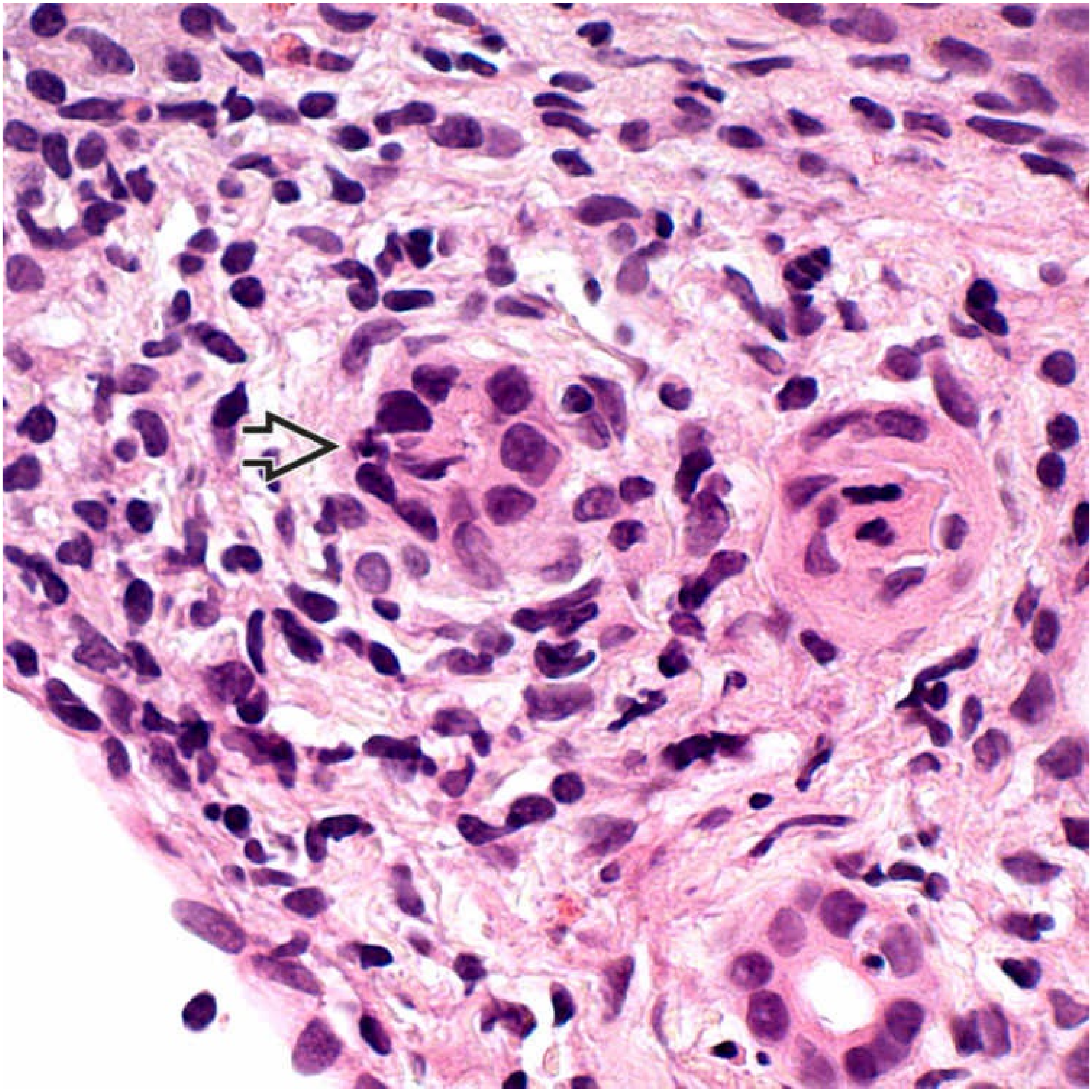
Centrilobular Cholestasis Due to NSAIDs
Centrilobular cholestasis and varying degrees of lobular inflammation, hepatocyte damage, and reactive hepatocellular changes can be seen in drug-induced cholangitis. This case is due to NSAID injury.



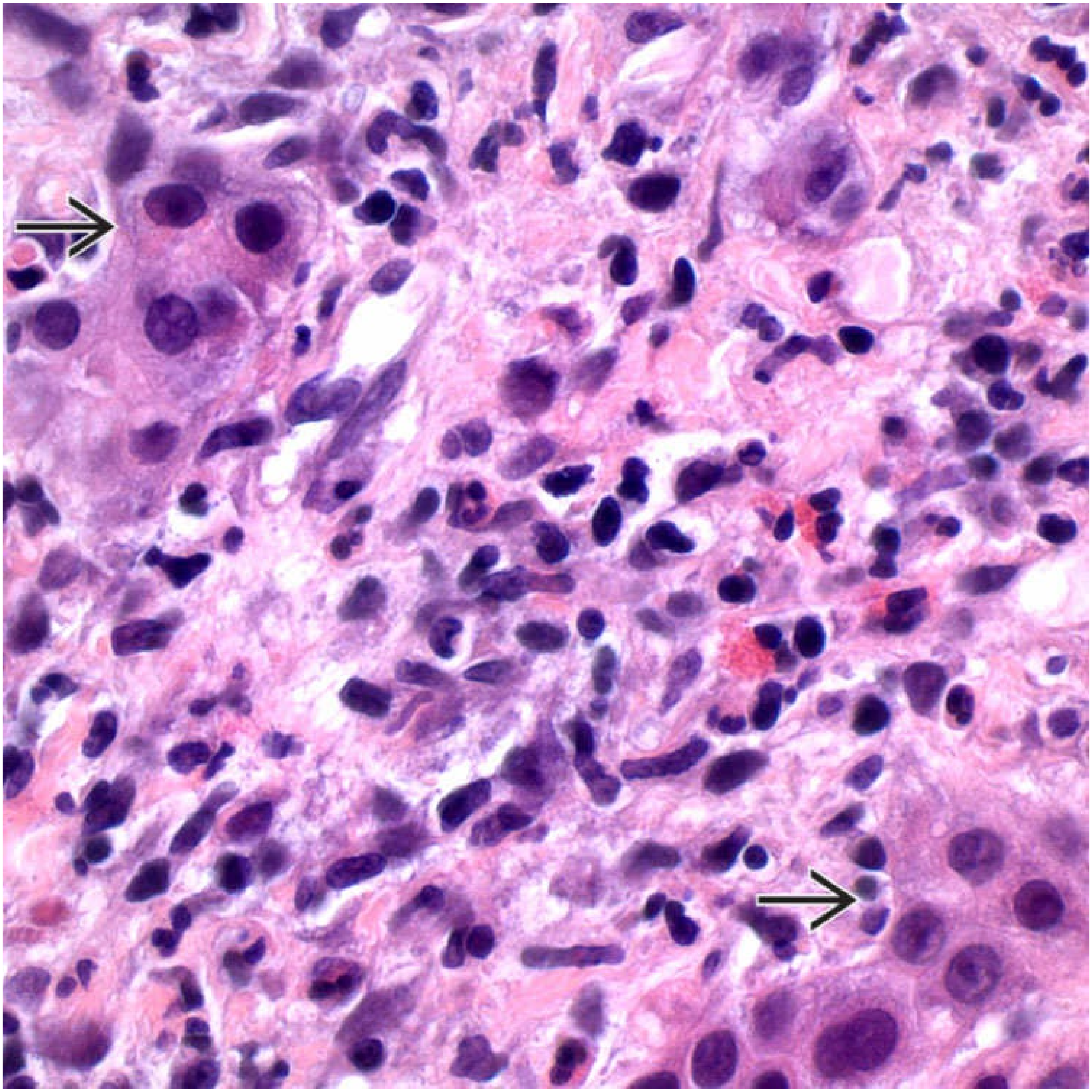
Canalicular Cholestasis
A high-power view shows canalicular cholestasis ➩ in zone 3, which is a common finding in drug-associated cholangitis.



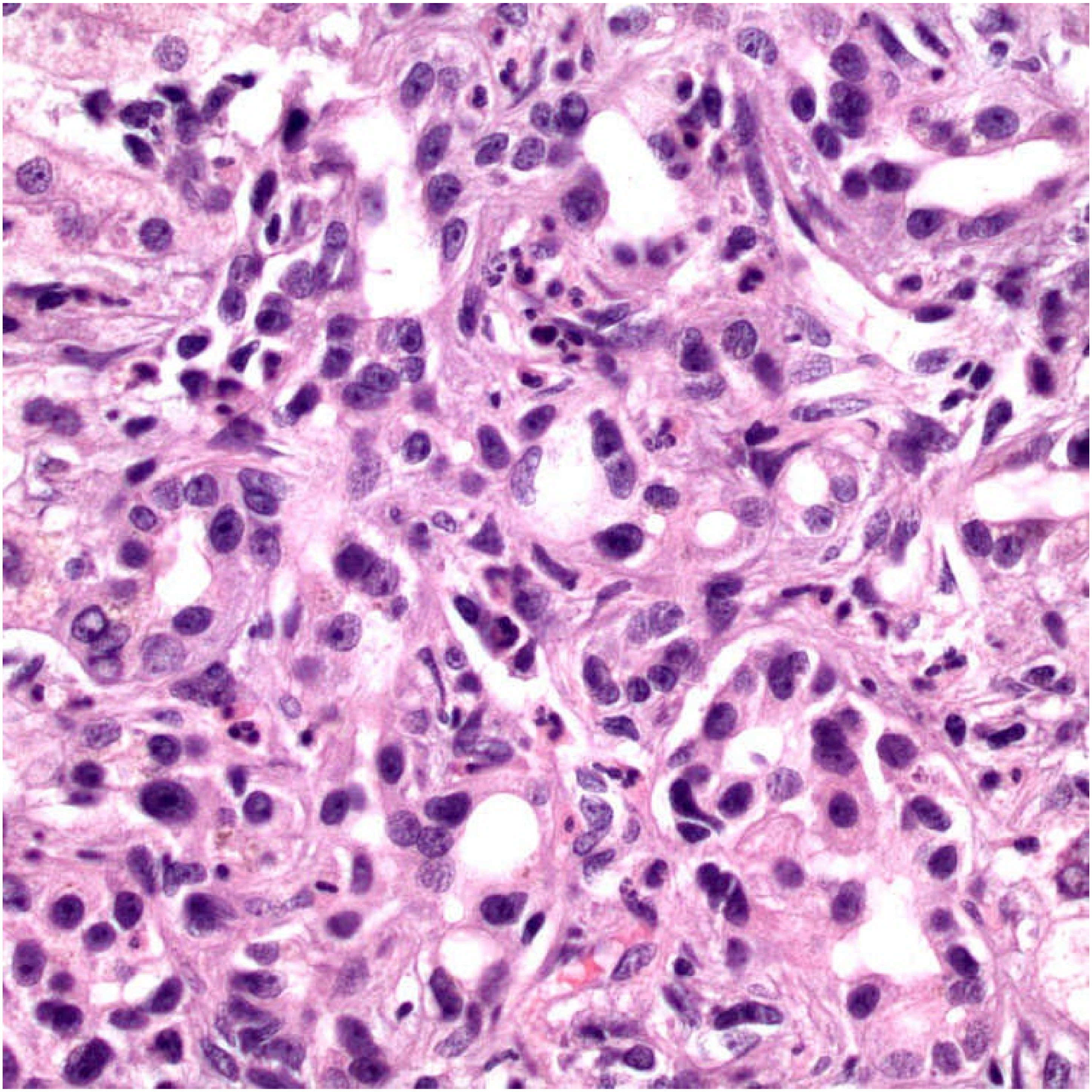
Mild Portal Inflammation and Duct Injury
This example of duct injury due to NSAIDs shows mild portal edema, a mild portal mononuclear cell infiltrate, and a damaged duct → with eosinophilic cytoplasm and variation in nuclear size.



Lymphocytic Infiltrate and Duct Injury
Portal tracts may be edematous, and the inflammatory infiltrate may be predominantly mononuclear or contain eosinophils. Note the damaged duct ➩ with eosinophilic cytoplasm and “jumbled” nuclei.

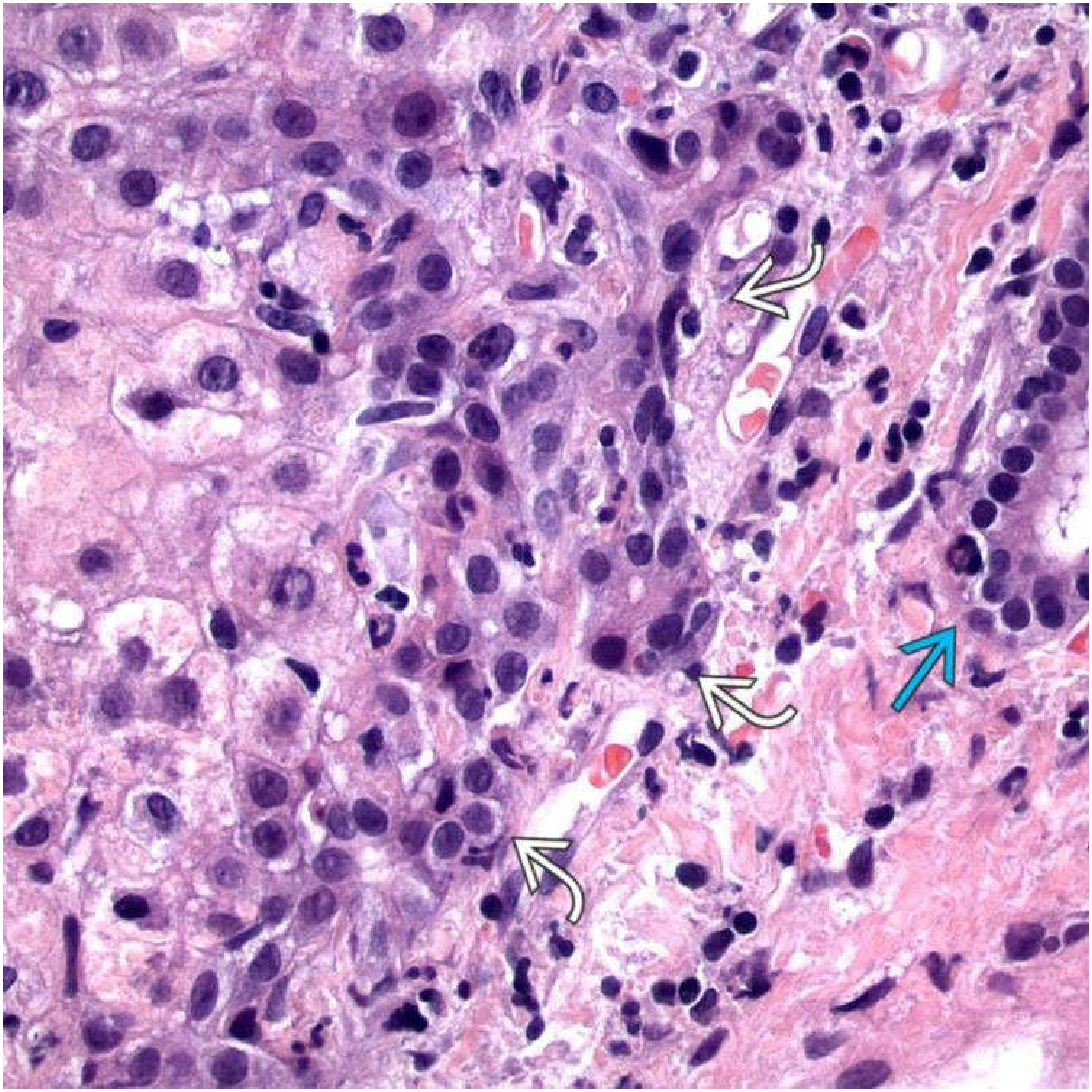


Mixed Portal Inflammation
The portal infiltrate may contain prominent eosinophils and plasma cells. Note the cholangiolar proliferation → at the edges of the portal tract.

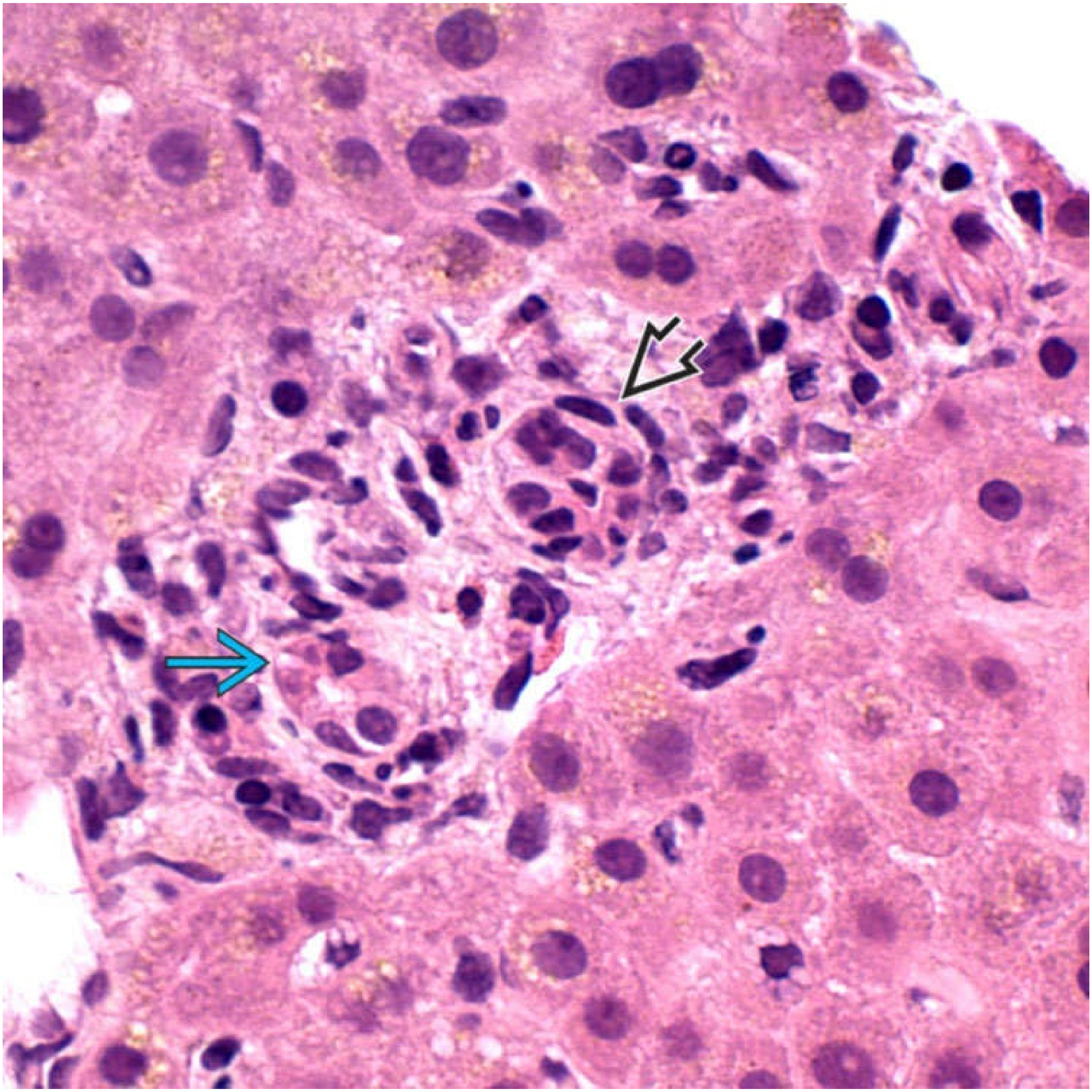


Ductular Reaction

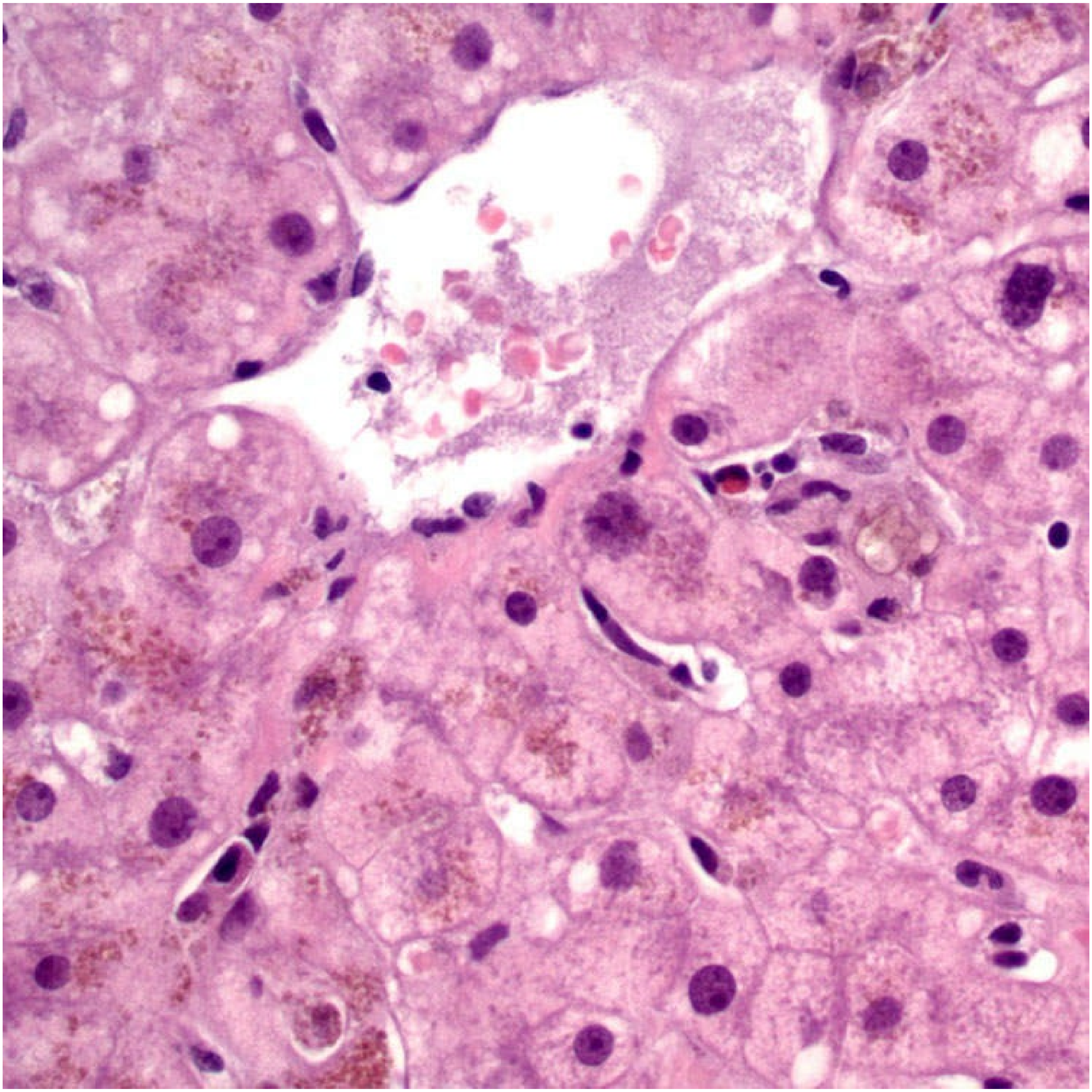
Patchy ductular reaction is a common finding in drug-associated cholangitis and duct injury.



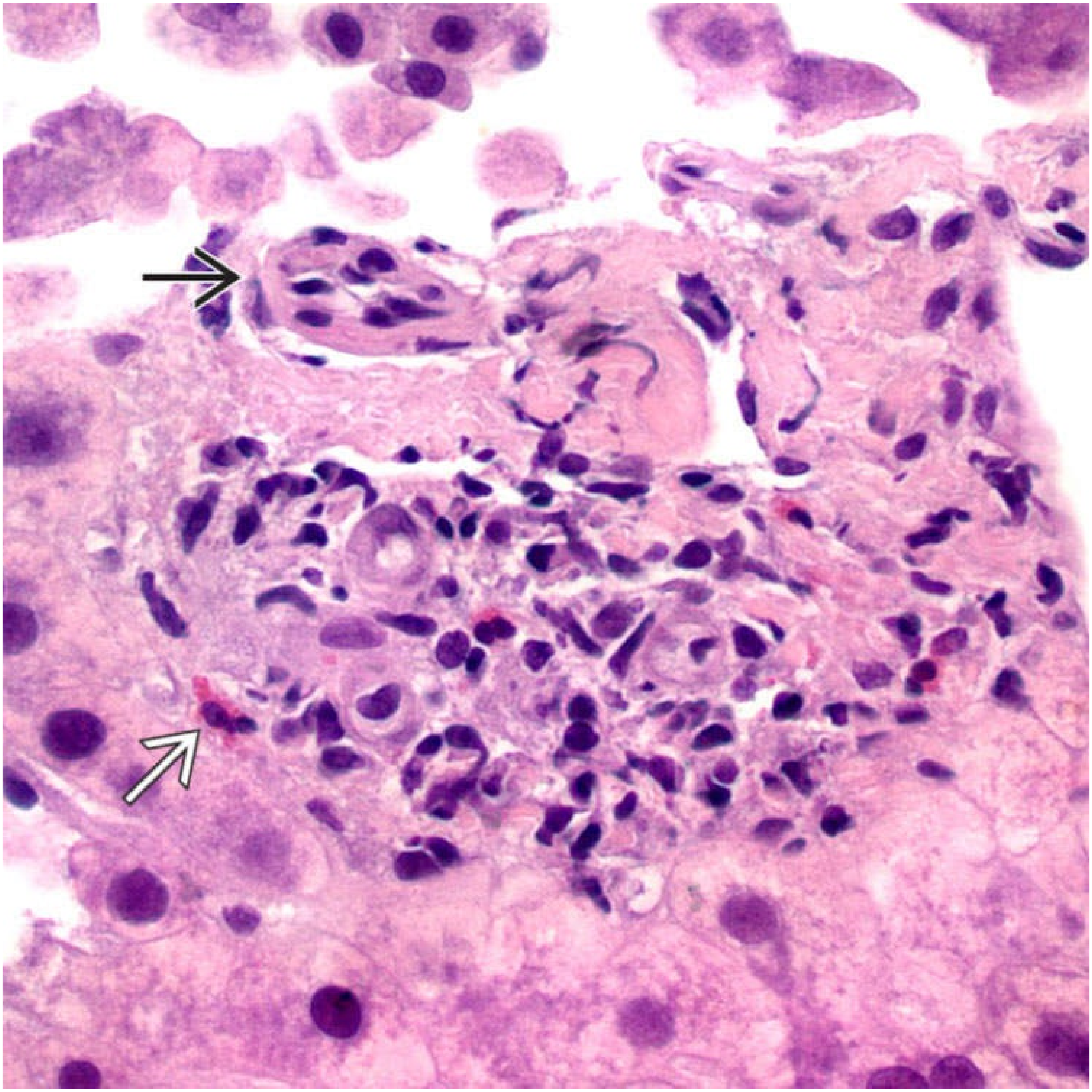
Ductular Reaction
Extensive bile ductular reaction is seen at the edge of this portal tract. The native bile duct is seen at the edge of the image.



Injured Bile Ducts Mild Portal Inflammation
The 2 bile ducts in this portal tract exhibit variation in nuclear shape and size and uneven spacing of nuclei →. One bile duct is also infiltrated by lymphocytes ⇨ .

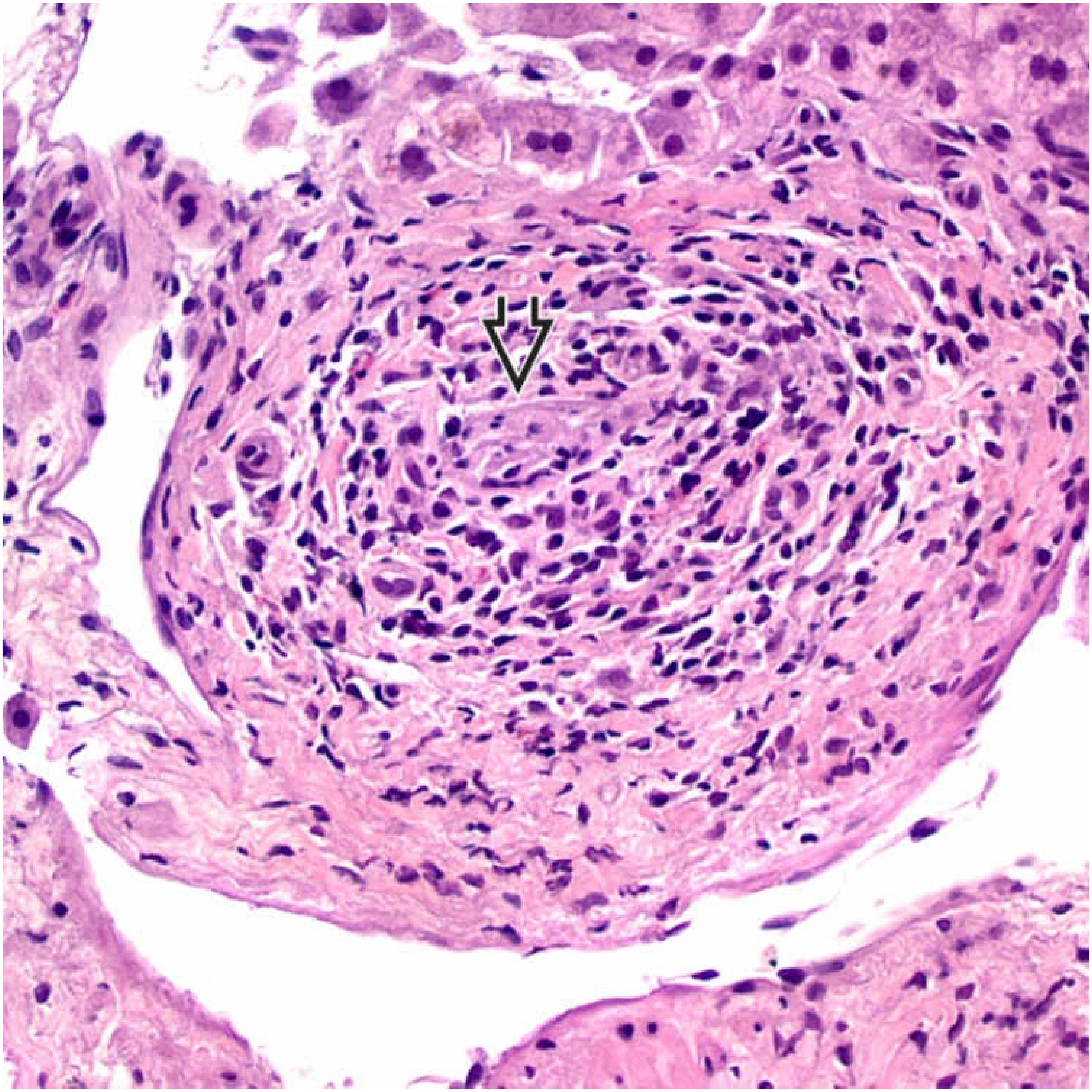


Centrilobular Cholestasis Secondary to Augmentin
This case of Augmentin-associated vanishing bile duct syndrome showed zone 3 cholestasis, a common finding in drug-related duct injury.

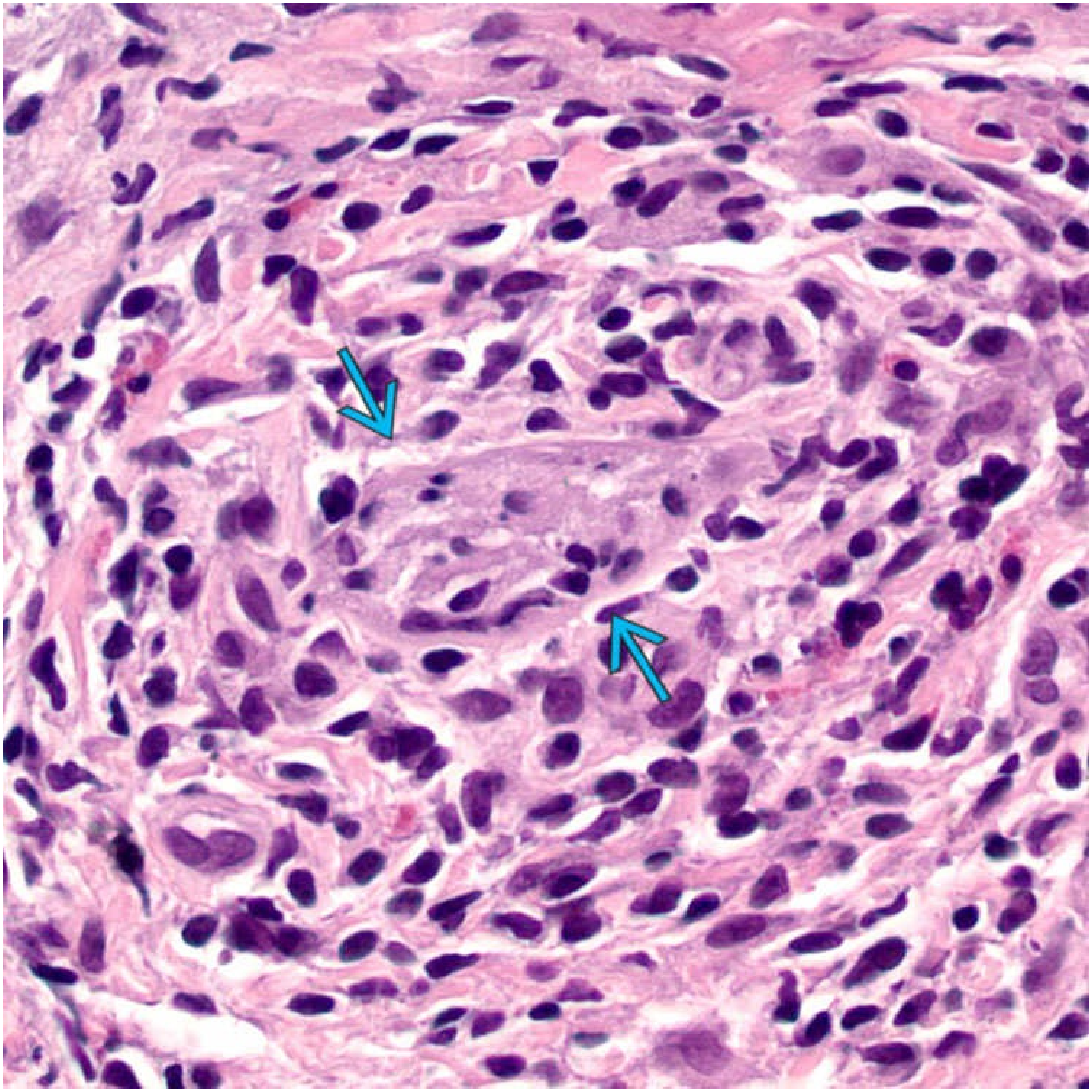


Bile Duct Loss

This portal tract in vanishing bile duct syndrome lacks a duct altogether. Note the unaccompanied hepatic arteriole → and the mononuclear cell portal infiltrate with admixed eosinophils ⇒ .



Markedly Damaged Duct
This portal tract from a case of Augmentin-associated vanishing bile duct syndrome shows a barely discernible bile duct remnant ➩ surrounded by mononuclear cells.



Duct Destruction
A high-power view of a portal tract from a case of Augmentin-associated vanishing bile duct syndrome shows duct destruction → and a predominantly mononuclear portal inflammatory infiltrate.

SELECTED REFERENCES

1. Levine, C, et al. Severe ductopenia and cholestasis from levofloxacin drug-induced liver injury: a case report and review. *Semin Liver Dis*. 2014; 34(2):246–251.

2. Bhamidimarri, KR, et al. Drug-induced cholestasis. *Clin Liver Dis*. 2013; 17(4):519–531. [vii].

3. Trauner, M, et al. MDR3 (ABCB4) defects: a paradigm for the genetics of adult cholestatic syndromes. *Semin Liver Dis*. 2007; 27(1):77–98.
4. Mohi-ud-din, R, et al. Drug- and chemical-induced cholestasis. *Clin Liver Dis*. 2004; 8(1):95–132. [vii].
5. Velayudham, LS, et al. Drug-induced cholestasis. *Expert Opin Drug Saf*. 2003; 2(3):287–304.

Stellate Cell Hyperplasia

KEY FACTS

Terminology

- Phenotypic changes in stellate cells as result of activation, most commonly due to vitamin A toxicity (hypervitaminosis A)
- Severity of liver disease depends on duration and dose of vitamin A

Etiology/Pathogenesis

- Overingestion of vitamin A

Clinical Issues

- Hepatomegaly often present
  - Varices, ascites if portal hypertension present
  - Jaundice variably present
- Cutaneous, gastrointestinal, neuroophthalmic, musculoskeletal, renal, hematological manifestations also common
- Nonspecific elevations in transaminases, alkaline phosphatase
- Plasma vitamin A levels may be normal

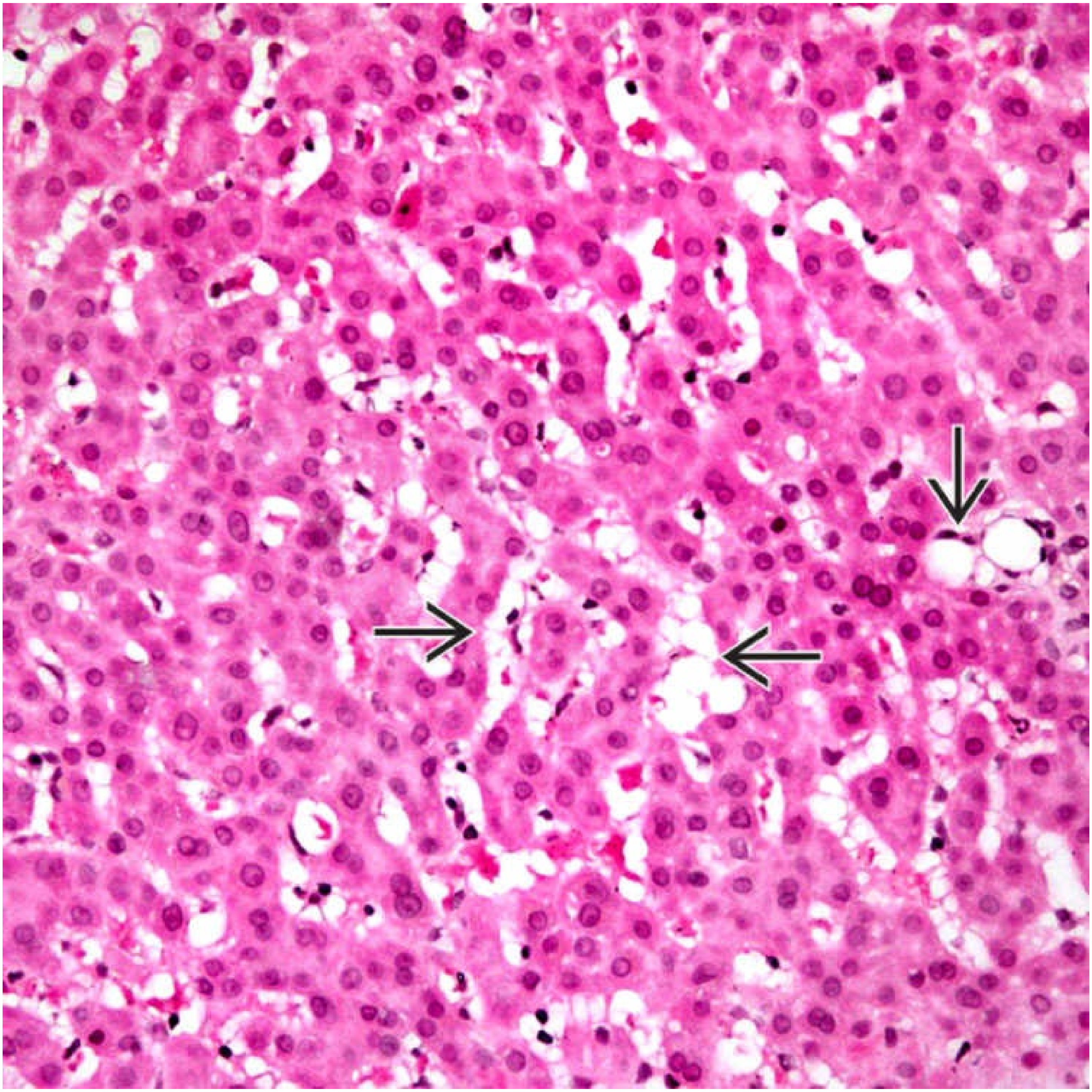
Microscopic

- Stellate cell hyperplasia and hypertrophy
- Hepatocellular injury, inflammation minor
- Fibrosis begins in perisinusoidal pattern, may progress to cirrhosis

Top Differential Diagnoses

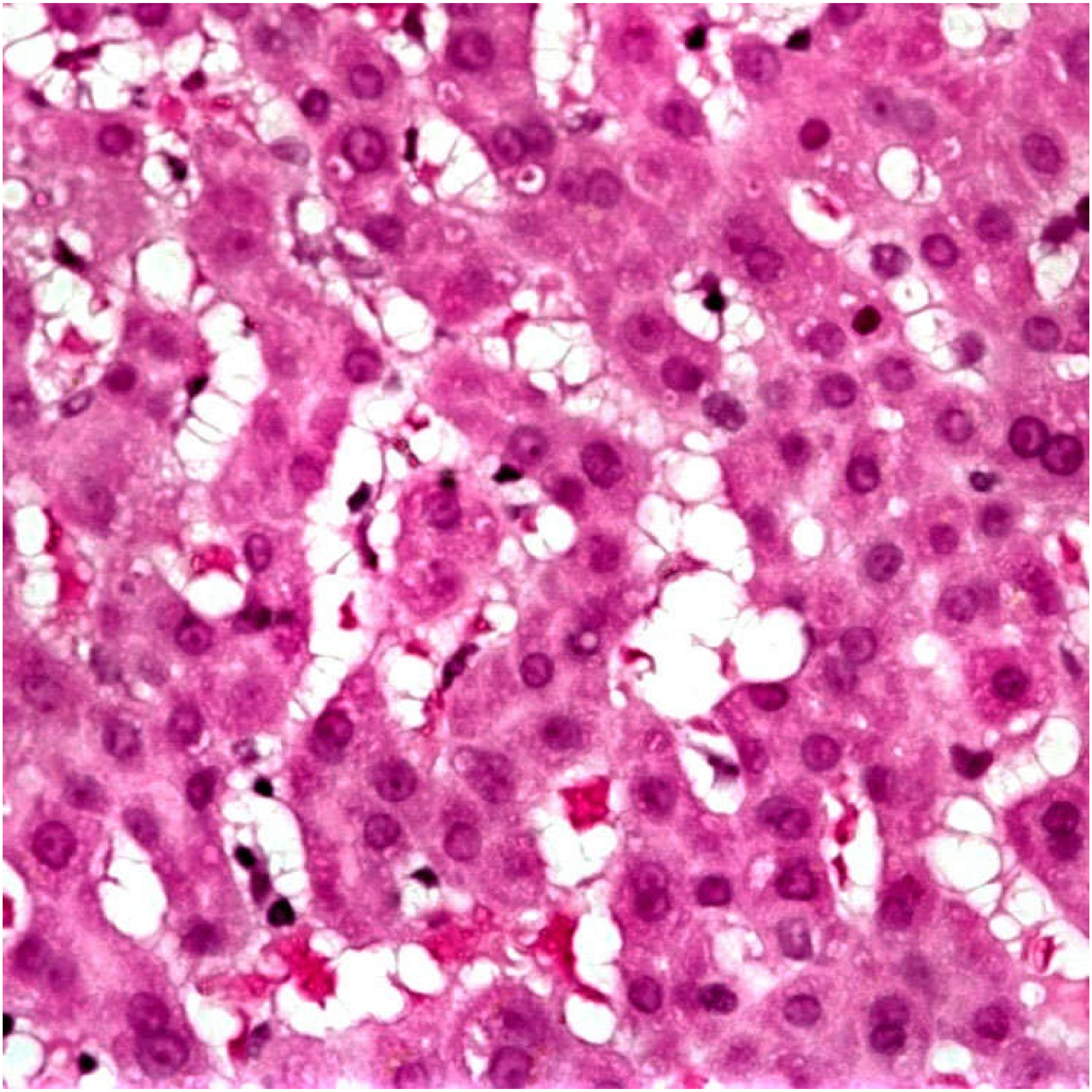
- Methotrexate therapy
- Steroid use
- IV fat emulsion administration

- Stellate cell activation has been reported in chronic viral hepatitis following transplantation
- May be marker of early fibrogenesis following transplantation

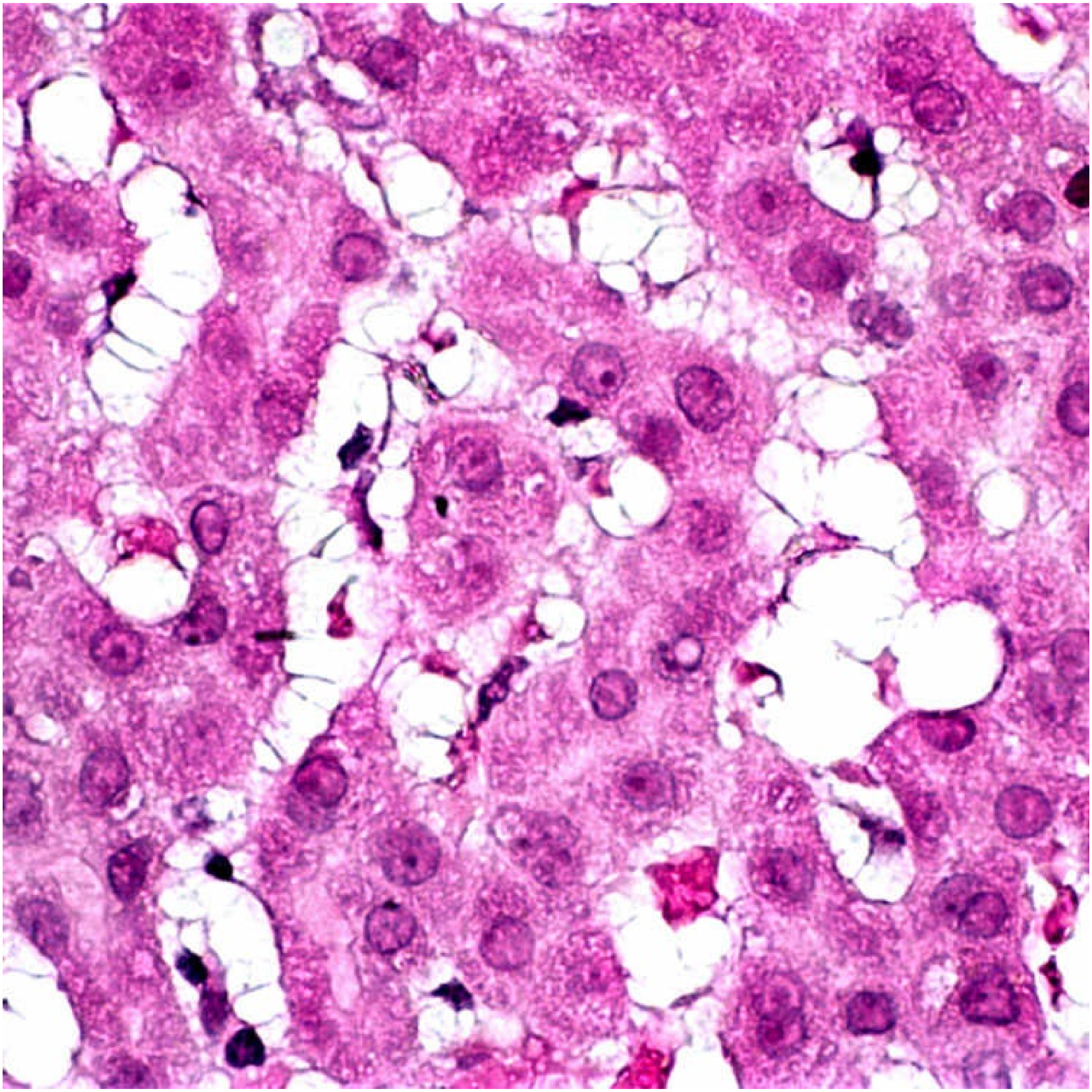


Hypervitaminosis

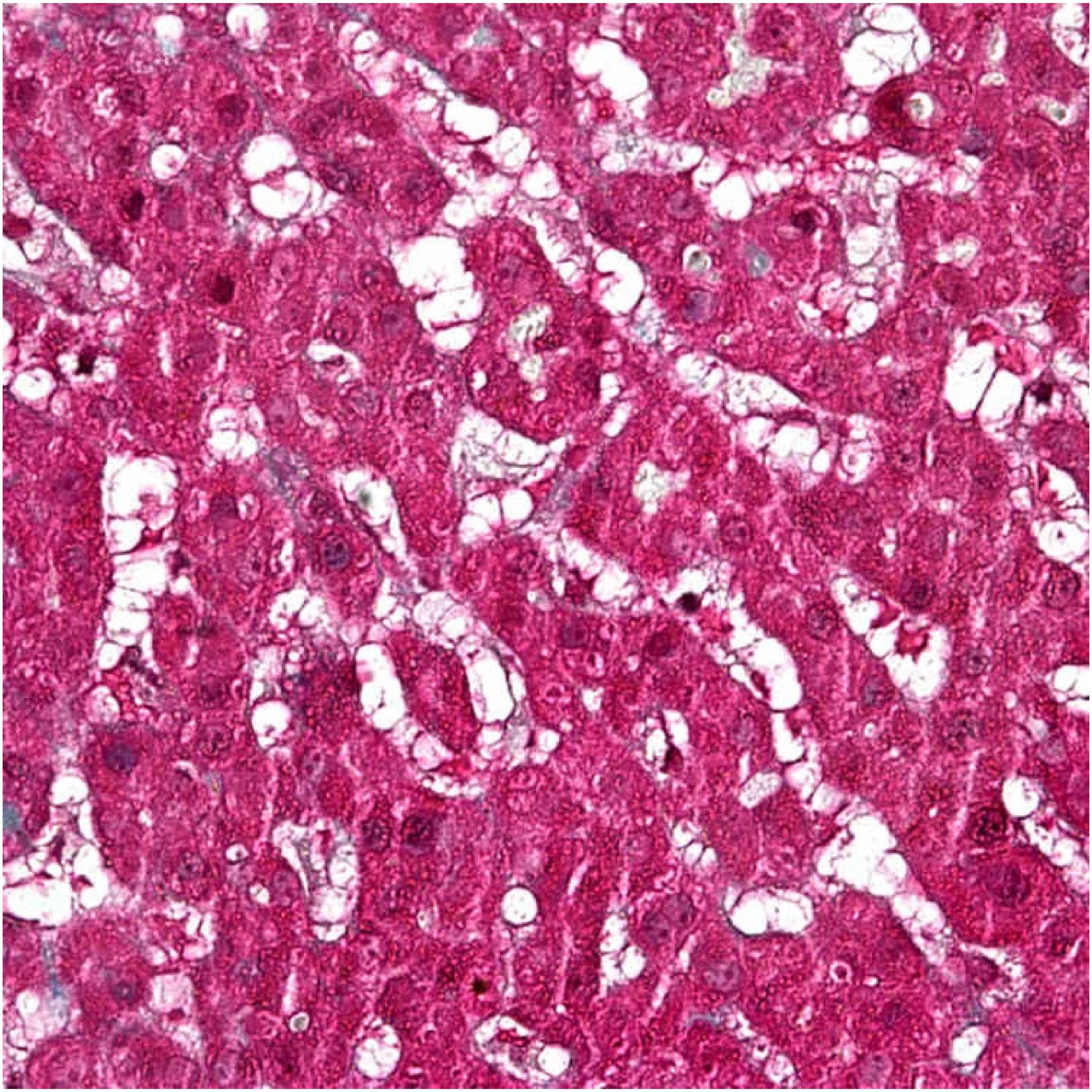
Low-power view of stellate cell hyperplasia in hypervitaminosis A illustrates bubbly, “multivacuolated” hepatic stellate cells in the sinusoids →. Note the lack of inflammation or hepatocyte degeneration.



Chronic Overingestion of Vitamin A
Hyperplastic, hypertrophic stellate cells are seen in the sinusoids of a patient who chronically overingested vitamin A supplements.



Hyperplastic and Hypertrophic Stellate Cells in Sinusoids
High magnification shows hyperplastic, hypertrophic stellate cells in the sinusoids with swollen, clear cytoplasm and delicate cytoplasmic processes.



Bubbly Cytoplasm of Stellate Cells
This patient does not have increased perisinusoidal fibrosis, but the contrast of the trichrome stain accentuates the bubbly cytoplasm of the stellate cells.

TERMINOLOGY

Abbreviations

- Hepatic stellate cells (HSC)

Synonyms

- Ito cell

- Perisinusoidal lipocyte

Definitions

- Phenotypic changes in stellate cells as result of activation
  - Most commonly seen in vitamin A toxicity (hypervitaminosis A)
    - Even moderate amounts of vitamin A can cause liver disease if taken over long period of time
- Stellate cells reside in space of Disse
  - Long cytoplasmic processes surround sinusoids
  - Contain small lipid droplets that are rich in vitamin A
  - Produce extracellular proteins
  - Play role in hepatic regeneration

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Overingestion of vitamin A
  - HSC are main site of vitamin A storage
  - Hepatotoxicity from overdose of vitamin A activates HSC
  - Activation causes sinusoidal obstruction, increased collagen synthesis

CLINICAL ISSUES

Presentation

- Very variable, many organ systems may be involved
  - Hepatomegaly
    - Varices, ascites if portal hypertension present
    - Jaundice variably present
  - Cutaneous, gastrointestinal, neuroophthalmic, musculoskeletal, renal, hematological manifestations also common
- Some patients asymptomatic
- Alcohol may potentiate toxic effects of vitamin A

Laboratory Tests

- Nonspecific elevations in transaminases, alkaline phosphatase
- Plasma vitamin A levels may be normal

Treatment

- Discontinue vitamin A ingestion

Prognosis

- Severity of liver disease depends on duration and dose of vitamin A
  - Cirrhosis or noncirrhotic portal hypertension due to sinusoidal fibrosis may develop
  - Fibrosis may continue after cessation given long half-life of vitamin A in liver
- Liver failure, cirrhosis at time of diagnosis portend worse prognosis

MICROSCOPIC

Histologic Features

- Stellate cell hyperplasia and hypertrophy
  - Enlarged cells with clear cytoplasm
  - Delicate cytoplasmic processes (multivacuolated appearance)
- Hepatocellular injury, inflammation minor
- Microvesicular steatosis may be present
- Fibrosis
  - Begins as perisinusoidal fibrosis
  - Usually panlobular
  - Central vein sclerosis has been described
  - May progress to cirrhosis
- Peliosis, periportal sinusoidal dilatation have been described
- Immunohistochemical markers
  - Vimentin
  - Desmin
  - Smooth muscle actin
  - GFAP
  - NCAM
  - Synaptophysin
- HSC have transient green fluorescence under ultraviolet light, particularly on frozen section

DIFFERENTIAL DIAGNOSIS

Methotrexate Therapy

- Should not have history of excessive vitamin A ingestion

Other Drugs

- Steroid use
  - Should not have history of excessive vitamin A ingestion
- IV fat emulsion administration

Posttransplant Biopsies

- Stellate cell activation has been reported in chronic viral hepatitis following transplantation

- May be marker of early fibrogenesis
- Should not have history of excessive vitamin A ingestion

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Histologic findings are subtle and easily missed

SELECTED REFERENCES

1. Mounajjed, T, et al. Clinical associations of hepatic stellate cell (HSC) hyperplasia. *Virchows Arch*. 2014; 465(1):57–65.
2. Nollevaux, MC, et al. Hypervitaminosis A-induced liver fibrosis: stellate cell activation and daily dose consumption. *Liver Int*. 2006; 26(2):182–186.
3. Carpino, G, et al. Alpha-SMA expression in hepatic stellate cells and quantitative analysis of hepatic fibrosis in cirrhosis and in recurrent chronic hepatitis after liver transplantation. *Dig Liver Dis*. 2005; 37(5):349–356.
4. Levine, PH, et al. Stellate-cell lipidosis in liver biopsy specimens. Recognition and significance. *Am J Clin Pathol*. 2003; 119(2):254–258.
5. Hautekeete, ML, et al. The hepatic stellate (Ito) cell: its role in human liver disease. *Virchows Arch*. 1997; 430(3):195–207.
6. Jorens, PG, et al. Vitamin A abuse: development of cirrhosis despite cessation of vitamin A. A six-year clinical and histopathologic follow-up. *Liver*. 1992; 12(6):381–386.
7. Geubel, AP, et al. Liver damage caused by therapeutic vitamin A administration: estimate of dose-related toxicity in 41 cases. *Gastroenterology*. 1991; 100(6):1701–1709.
8. Leo, MA, et al. Hypervitaminosis A: a liver lover's lament. *Hepatology*. 1988; 8(2):412–417.

SECTION 6
FATTY LIVER DISEASES

OUTLINE

Alcoholic Liver Disease

KEY FACTS

Terminology

- Hepatocyte injury and inflammation resulting from chronic alcohol consumption
  - Wide spectrum of disease ranging from subclinical to end-stage liver disease
  - ~ 20-40% of chronic alcoholics who undergo biopsy have histologic evidence of alcoholic liver disease (ALD)

Clinical Issues

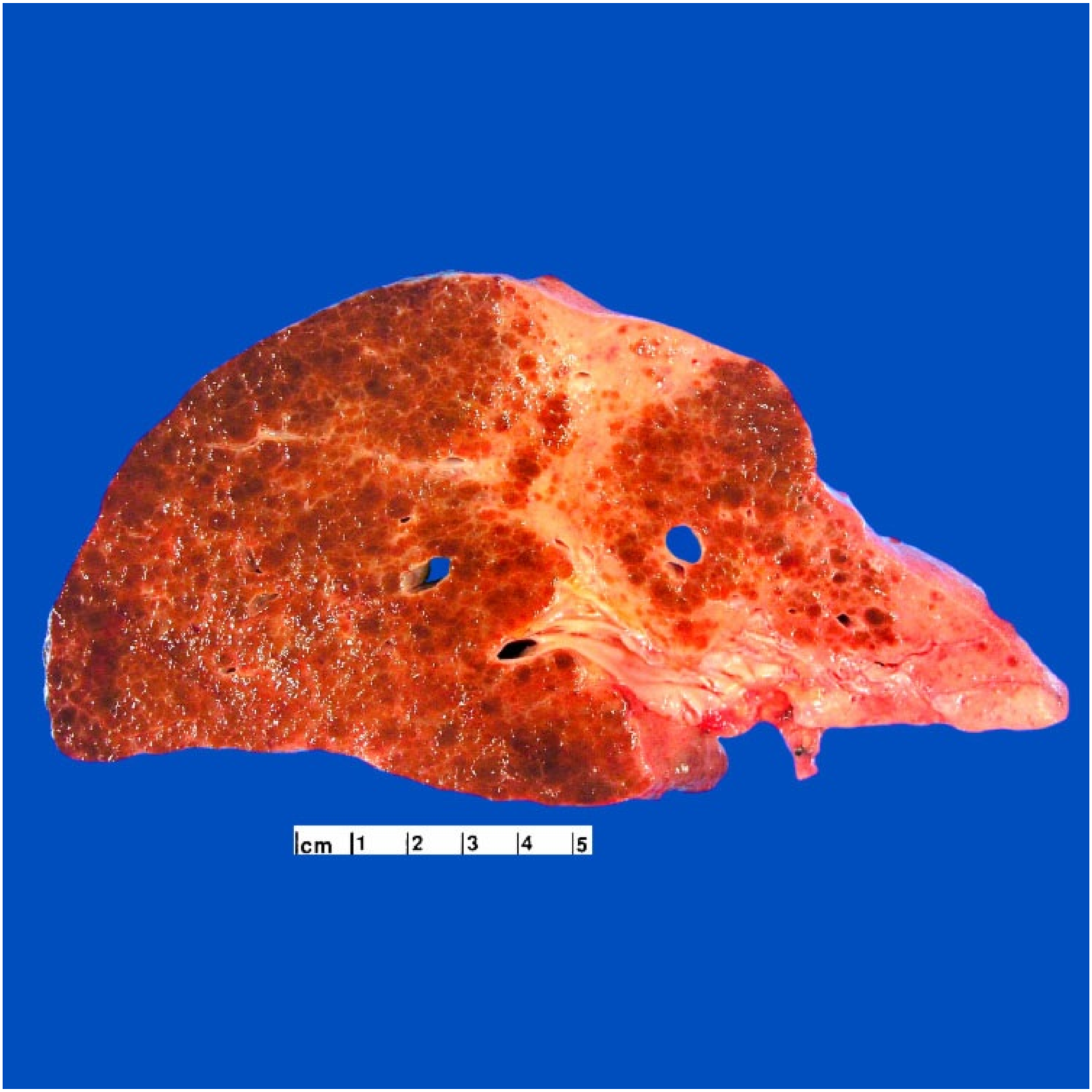
- Very variable presentation
- Moderately elevated transaminases (AST/ALT ratio typically >2)

Microscopic

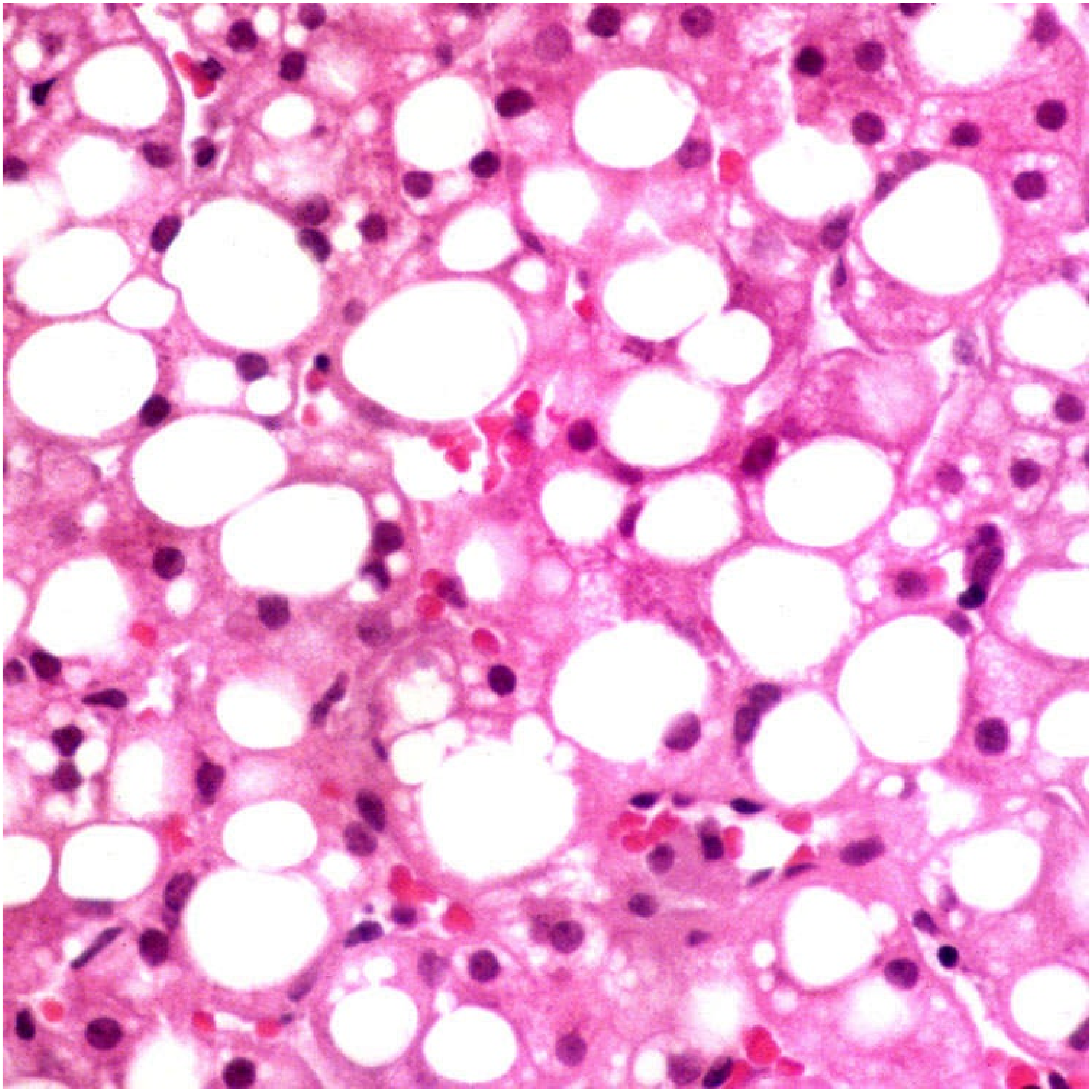
- Combination of hepatocyte injury, inflammation, steatosis, and fibrosis
  - Hepatocytic ballooning
  - Lobular inflammation with predominance of neutrophils
  - Mallory-Denk bodies (Mallory hyaline)
  - Megamitochondria
  - Steatosis
  - Fibrosis
  - – Most often pericellular and perivenular, especially initially
- Cholestatic features may be seen
- Iron deposition in hepatocytes and Kupffer cells is common

Top Differential Diagnoses

- Nonalcoholic steatohepatitis (NASH)
  - Histology of ALD and NASH virtually identical; favor ALD when Mallory bodies, neutrophil aggregates, or sclerosing hyaline necrosis is present
- Chronic hepatitis C
  - Many patients have both ALD and hepatitis C infection

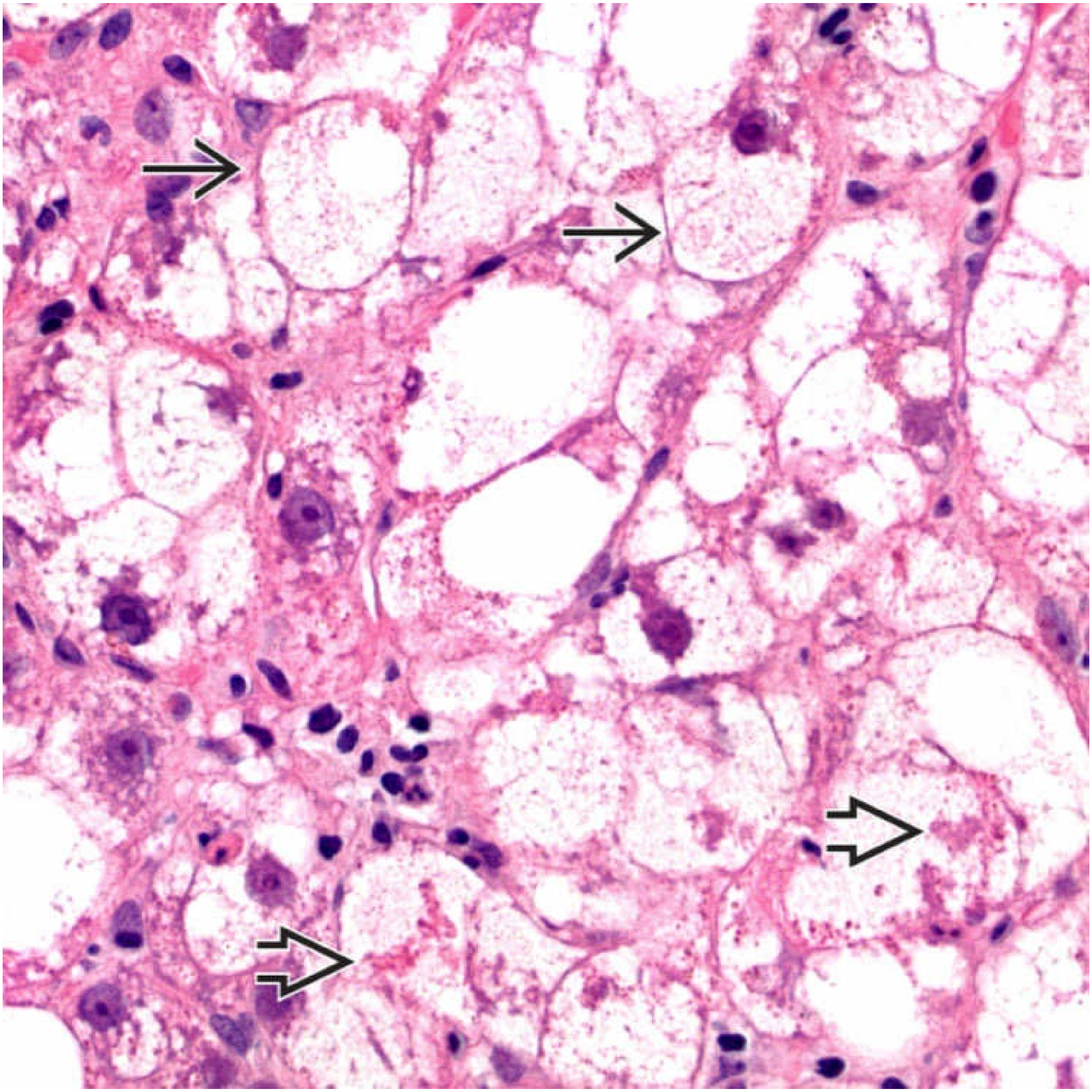


Gross Appearance
This explant from a patient with end-stage alcohol-induced cirrhosis shows a brown, tan, fibrotic, and nodular cut surface.

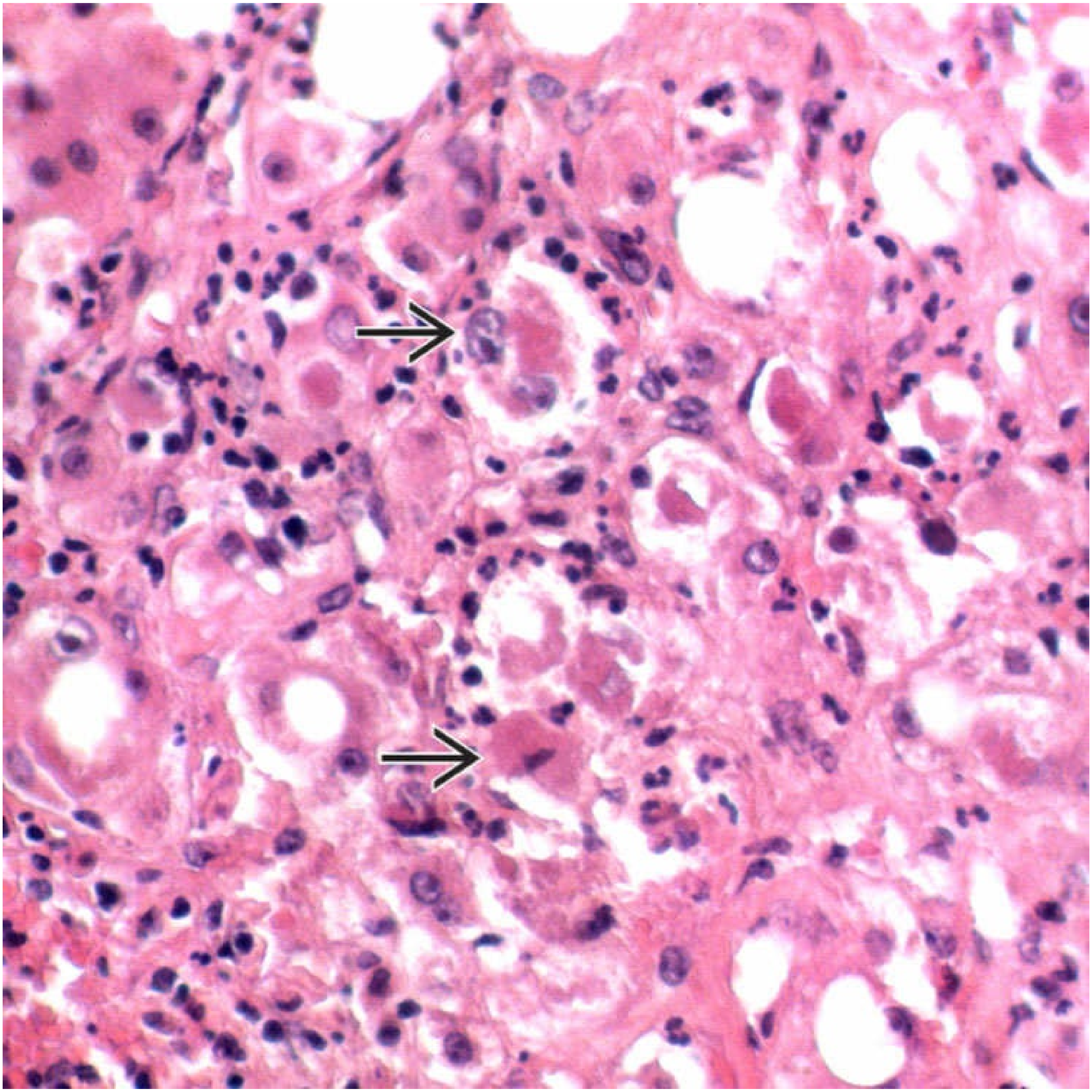


Steatosis

Steatosis, most often macrovesicular (large droplets of fat within the hepatocytes that commonly push the nuclei to the periphery of the cytoplasm), is a typical finding in alcoholic liver disease (ALD).



Hepatocyte Ballooning
This high-magnification photomicrograph shows ballooned hepatocytes → with rarefied, clumped cytoplasm and Mallory-Denk bodies ⇨ typical of alcoholic steatohepatitis.



Mallory-Denk Bodies
Ballooned hepatocytes → containing many Mallory-Denk bodies are typical in alcoholic steatohepatitis, along with lobular inflammation featuring satellitosis of neutrophils around the ballooned cells.

TERMINOLOGY

Abbreviations

• Alcoholic liver disease (ALD)

Definitions

• Hepatocyte injury and inflammation resulting from chronic alcohol consumption

- Wide spectrum of clinical and pathologic disease ranging from mild/subclinical to end-stage cirrhosis and death

ETIOLOGY/PATHOGENESIS

Alcohol Consumption

- Alcohol is direct hepatotoxin
- Both genetic and environmental factors determine susceptibility to liver injury

CLINICAL ISSUES

Epidemiology

- Incidence
  - ~ 20-40% of chronic alcoholics who undergo biopsy have histologic evidence of ALD

Presentation

- Very variable
  - Anorexia, nausea, vomiting, abdominal pain/tenderness, hepatomegaly
  - Variably present jaundice
- Some patients are asymptomatic
- End-stage patients may have encephalopathy, ascites, coagulopathy, varices

Laboratory Tests

- Moderately elevated transaminases (AST/ALT ratio typically >2)
- Variably elevated alkaline phosphatase, bilirubin
- Hypoalbuminemia, prolonged PTT in end-stage disease

Treatment

- Abstinence
- Liver transplant

Prognosis

- Very variable course of disease

MICROSCOPIC

Histologic Features

- Combination of hepatocyte injury, inflammation, steatosis, and fibrosis

- ○ Hepatocyte ballooning degeneration
  - – Enlarged, swollen, pale, flocculent and clumped cytoplasm

○ Acidophil bodies

○ Mallory-Denk bodies (Mallory hyaline)

– Discrete masses of ropy eosinophilic material

– Neither invariably present or specific

○ Megamitochondria

○ Inflammation

– Neutrophils are principal inflammatory cell

– Encircle Mallory-Denk body-bearing cells (satellitosis)

– Lobular inflammation usually > portal inflammation

○ Steatosis

– Almost always present but can be absent depending on timing of biopsy

– Usually macrovesicular, can be mixed with microvesicular, or rarely pure microvesicular (foamy degeneration)

– Often begins in zone 3

○ Fibrosis

– Pericellular/perisinusoidal fibrosis: Chicken wire pattern of fibrosis that surrounds hepatocytes

– Perivenular fibrosis around central veins

– Eventual progression to bridging fibrosis and cirrhosis

○ Cholestasis and cholangiolitis may be seen

– May be mistaken for large bile duct obstruction

○ Iron deposition frequent, especially in cirrhosis

○ Lymphocytic phlebitis and obliterative fibrosis of terminal hepatic venule

○ Glycogenated nuclei

- Sclerosing hyaline necrosis
  - ○ Hepatocytic necrosis, dense perivenular/perisinusoidal fibrosis, and obliteration of terminal hepatic venules
  - ○ May be associated with noncirrhotic portal hypertension

DIFFERENTIAL DIAGNOSIS

Nonalcoholic Steatohepatitis

- Metabolic syndrome, such as diabetes, obesity, hyperlipidemia

- No history of alcohol use
- Cholestatic features, sclerosing hyaline necrosis, lymphocytic phlebitis uncommon
- Glycogenated nuclei uncommon in ALD

Chronic Hepatitis C

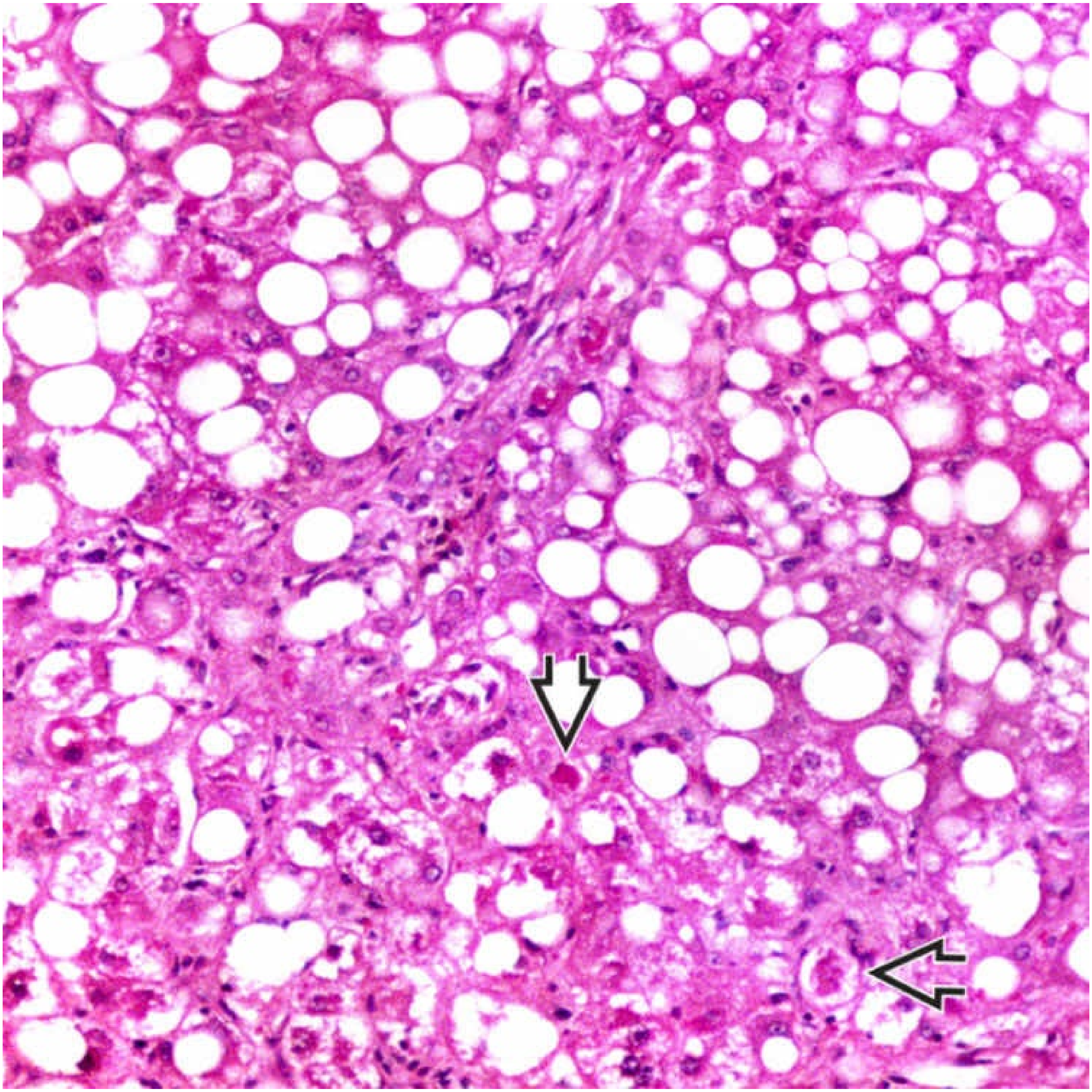
- Both ALD and hepatitis C virus (HCV) show steatosis, but distribution is more random rather than zonal in HCV
- HCV usually has more portal inflammation, fewer neutrophils
- ALD and chronic HCV may coexist in many patients

Drug Toxicity

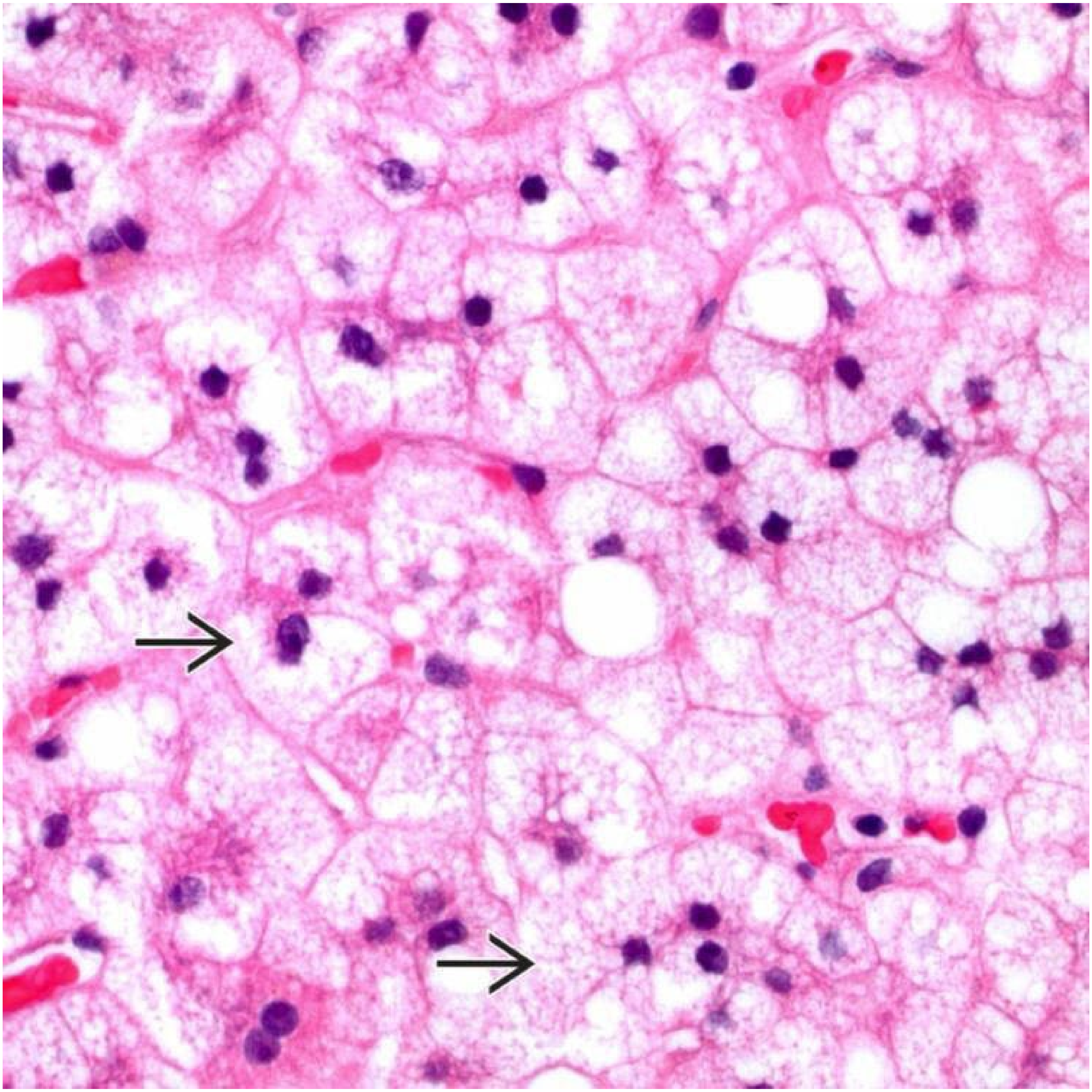
- History of drug use temporally corresponding to onset of disease
- Eosinophils may be prominent
- Amiodarone in particular may closely mimic ALD

Biliary Obstruction

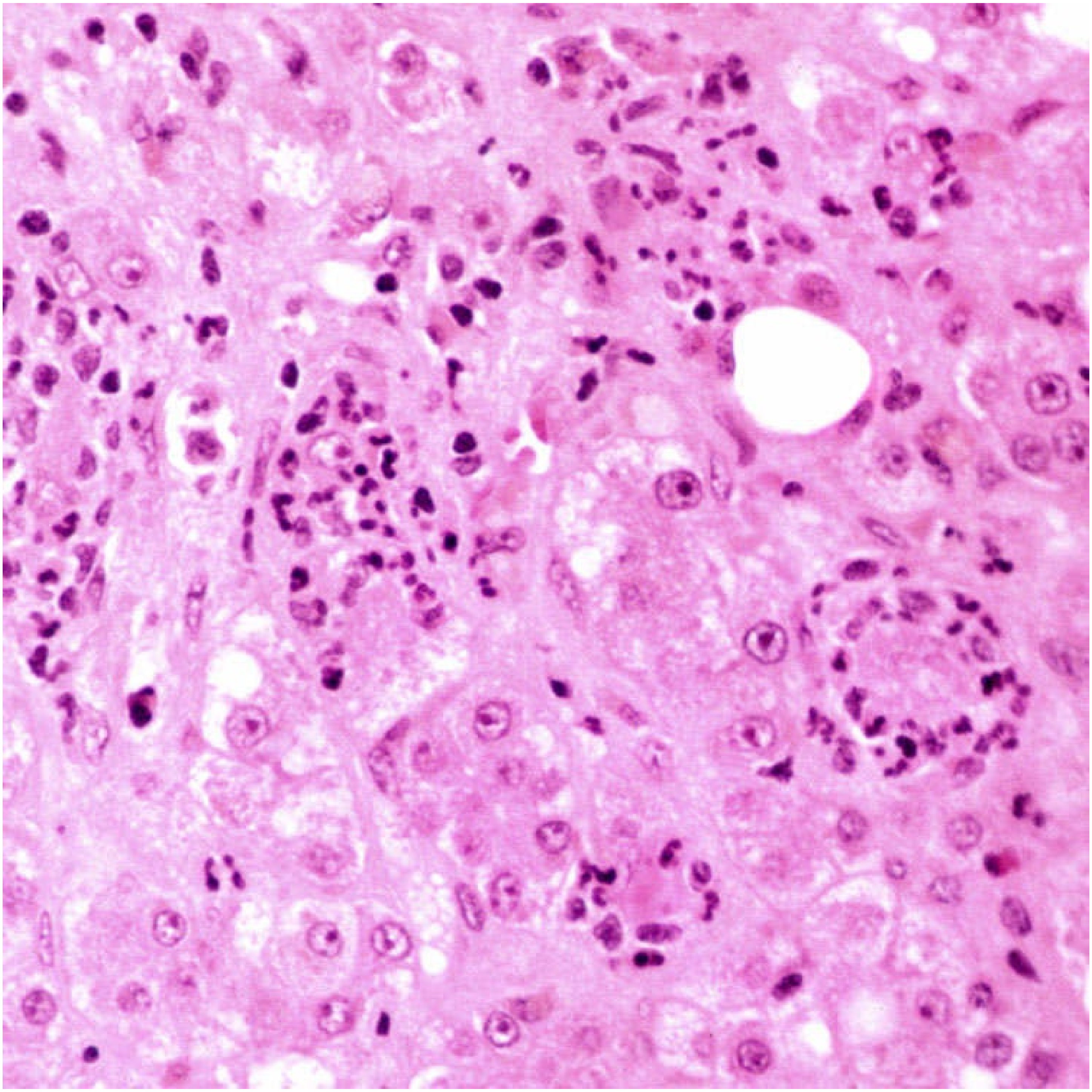
- Bile ductular reaction with associated neutrophilic infiltrate is common
- Abnormal ERCP or image studies



Typical Features
Marked macrovesicular steatosis, lobular inflammation, and ballooned hepatocytes are common findings in alcoholic steatohepatitis. Numerous Mallory-Denk bodies are also visible .

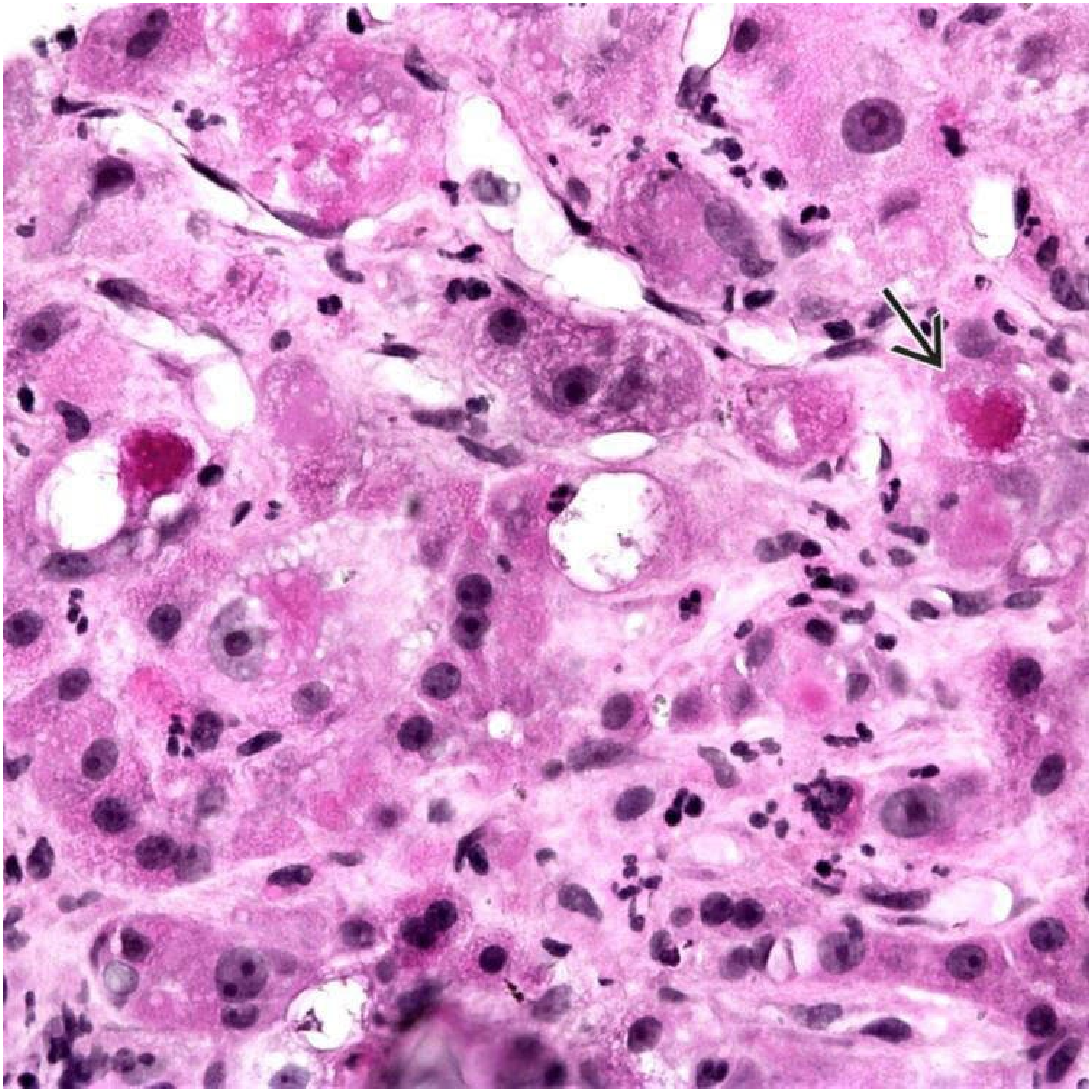


Microvesicular Fat
This case of ALD shows microvesicular steatosis with focally swollen hepatocytes → and centrally located nuclei. The fat in ALD is usually macrovesicular, but it may be mixed with microvesicular as seen here.



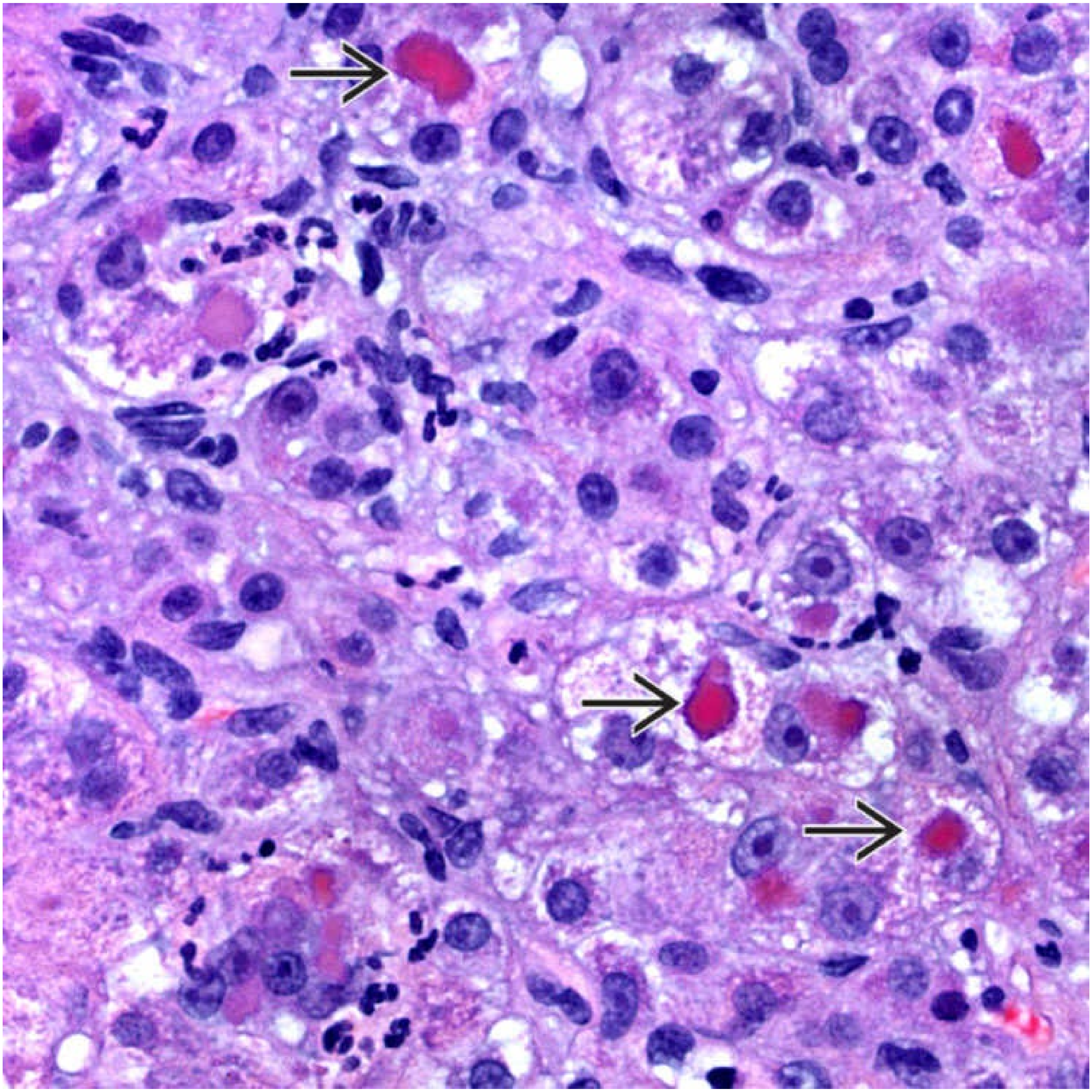
Satellitosis

Aggregates of neutrophils are frequently seen in alcoholic steatohepatitis but are uncommon in NASH. When the neutrophils surround Mallory-Denk bodies or necrotic hepatocytes, it is termed “satellitosis.”



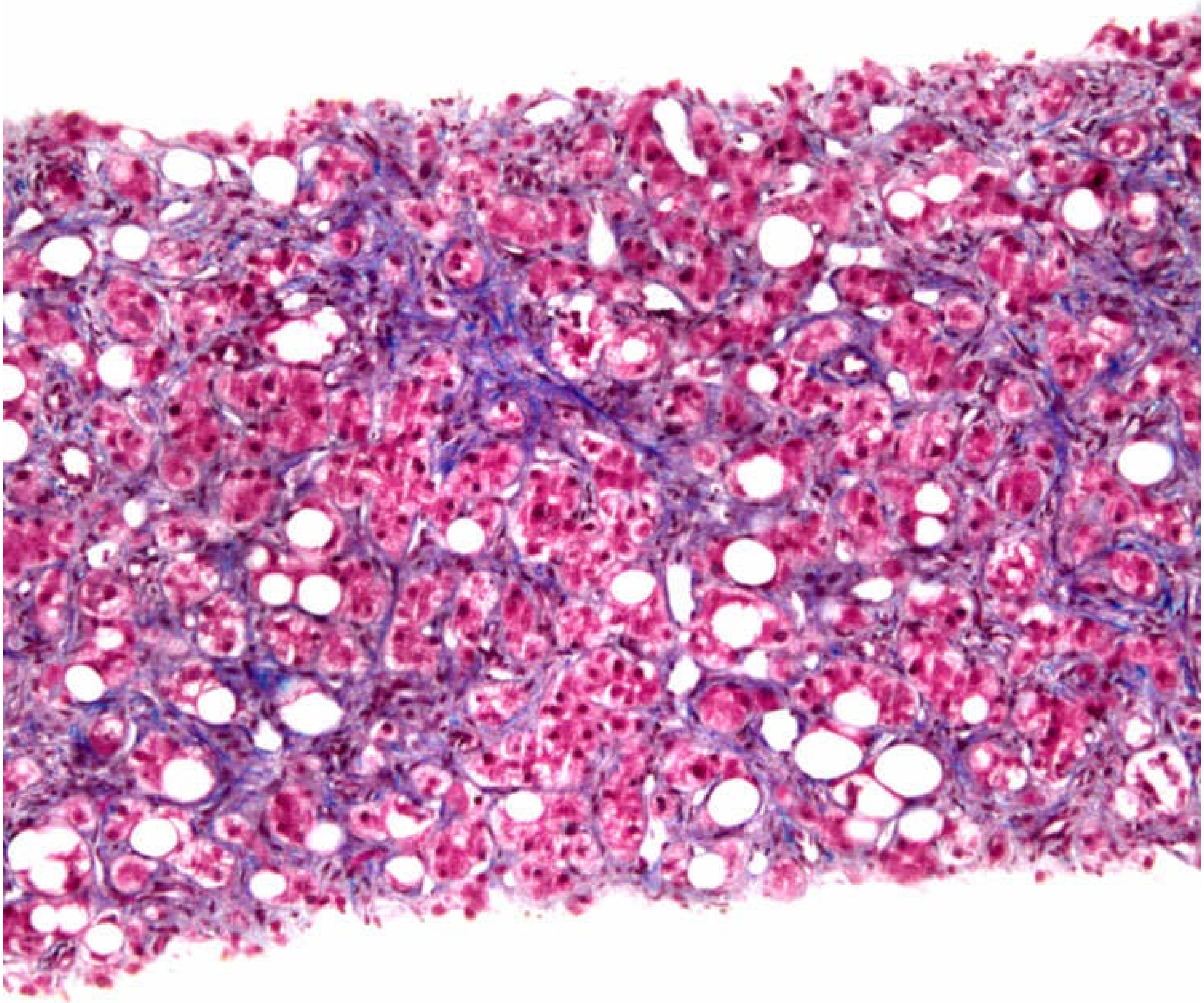
Mallory-Denk Bodies

Mallory-Denk bodies → are the eosinophilic, ropy, & branching substance composed of intermediate filaments in cytoplasm of injured hepatocytes in alcoholic steatohepatitis. Although Mallory-Denk bodies may also be seen in NASH, ALD should be suspected when abundant.

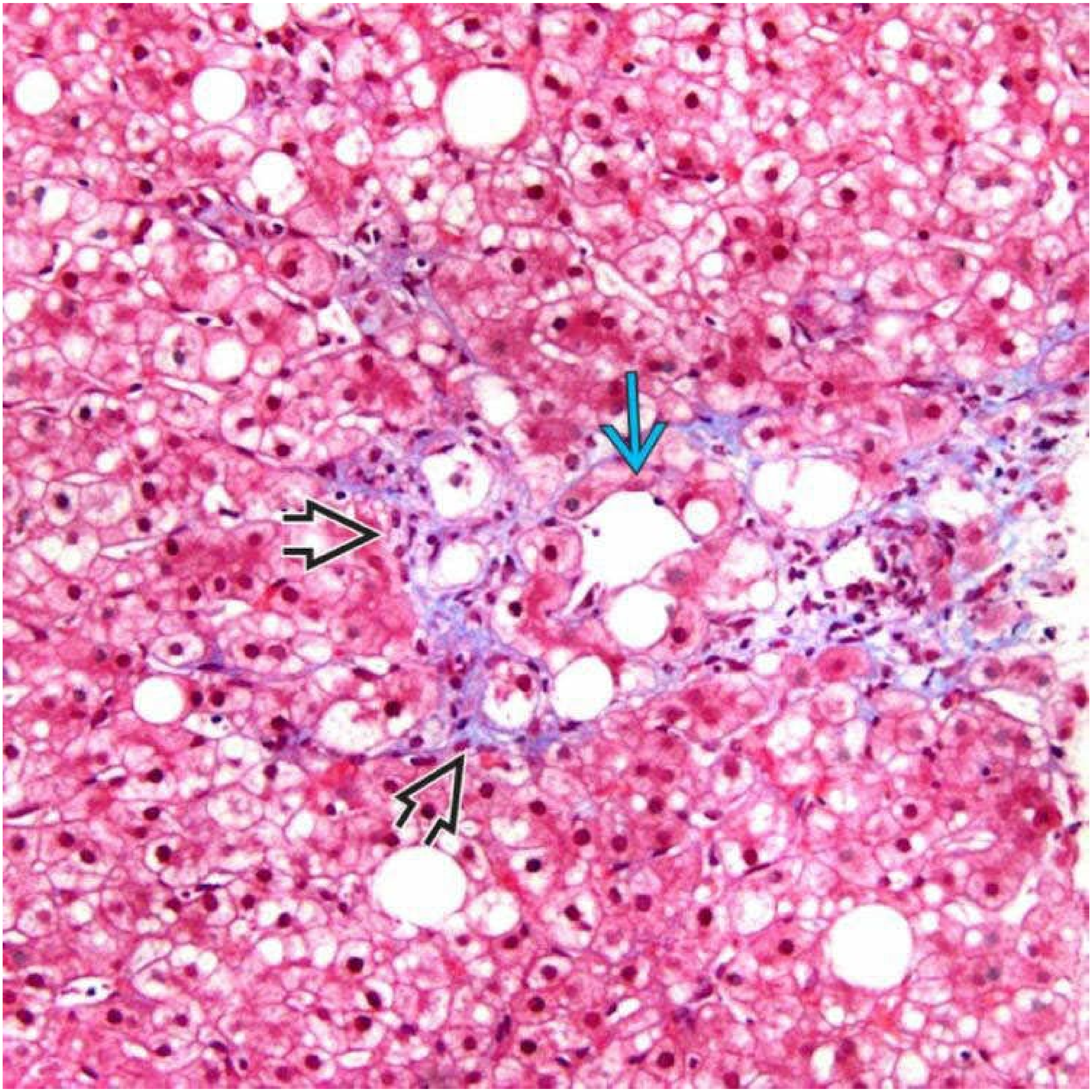


Megamitochondria

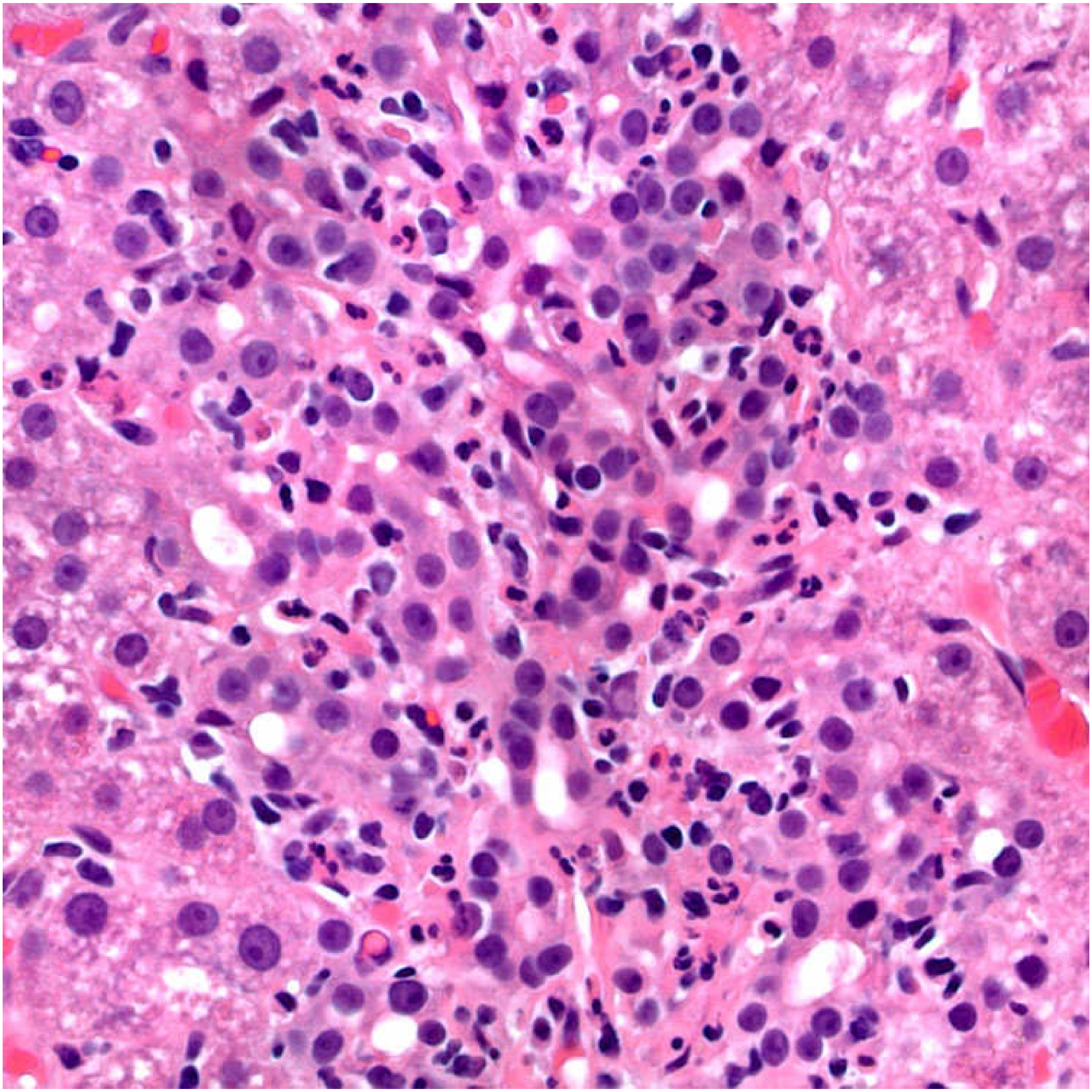
Megamitochondria → consist of round, oblong, and eosinophilic inclusions in the hepatocytes.



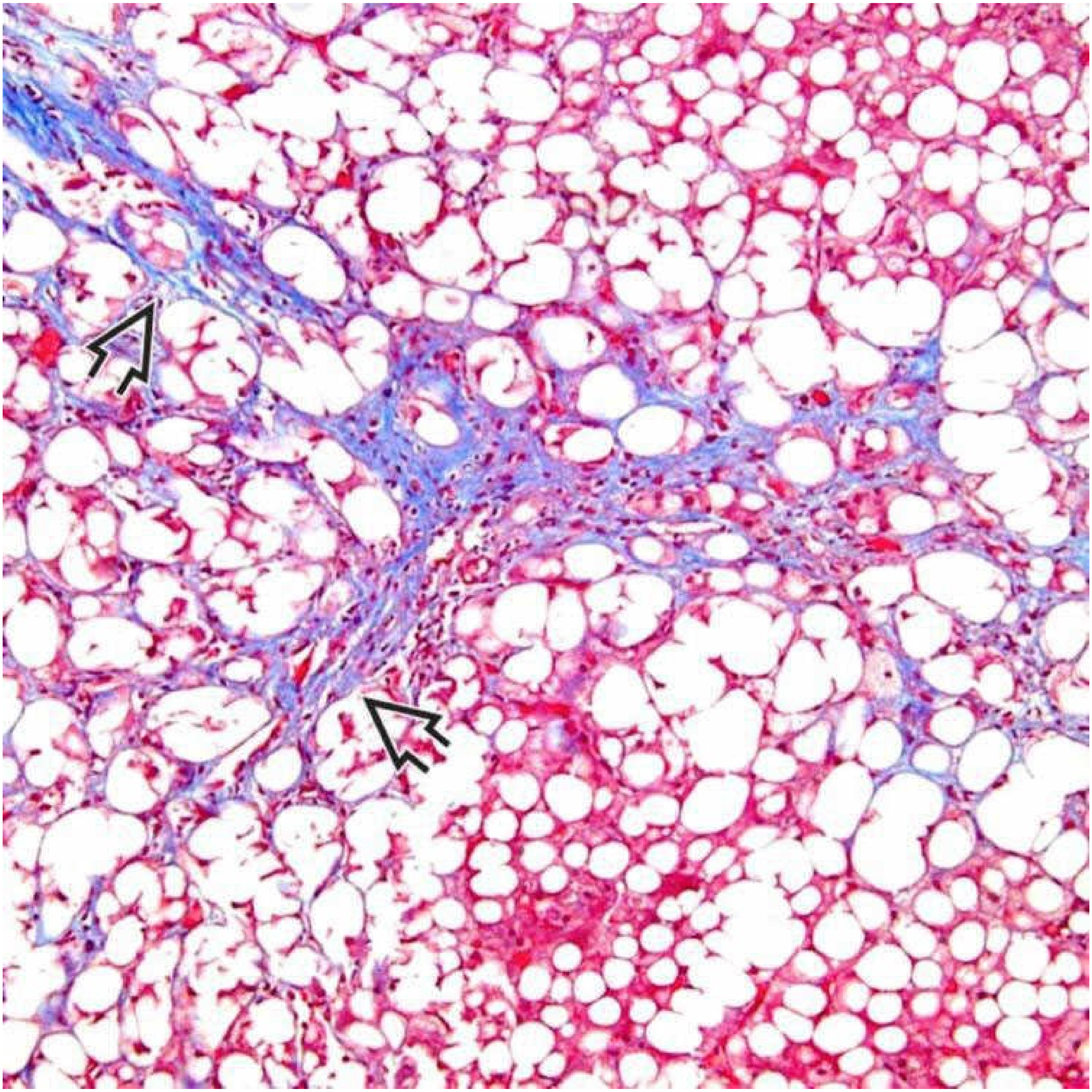
Fibrosis
Collagen fiber deposition within the sinusoidal spaces (chicken wire or pericellular fibrosis) is common in ALD. This pattern of fibrosis is also a feature in NASH.



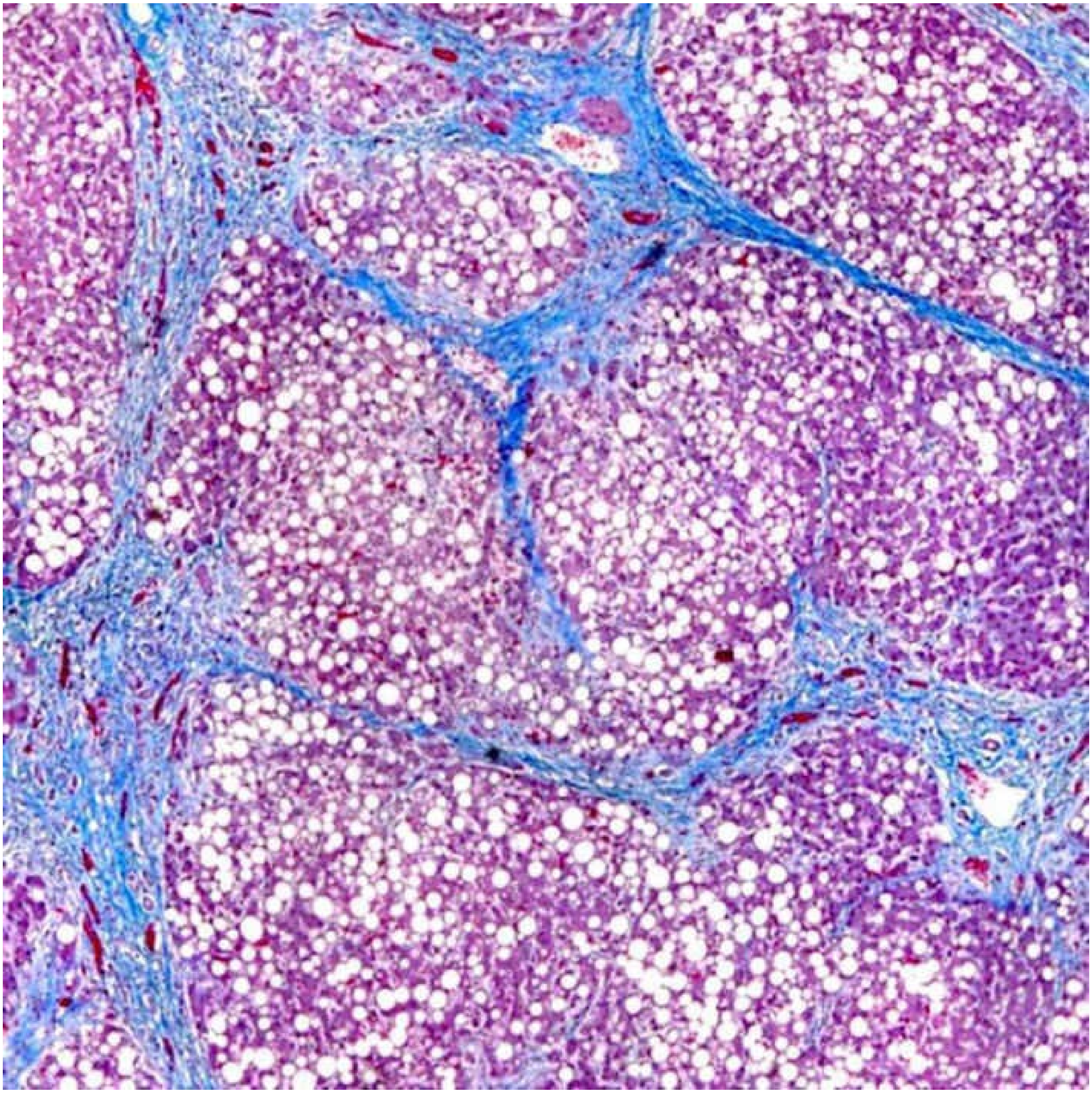
Fibrosis
The fibrosis in early ALD typically begins around the central vein. Note the focal areas of pericellular fibrosis in zone 3 .



Ductular Reaction
Some cases of ALD have bile ductular reaction with an associated neutrophilic infiltrate that can mimic large bile duct obstruction. Cholestasis can also be seen in these cases.

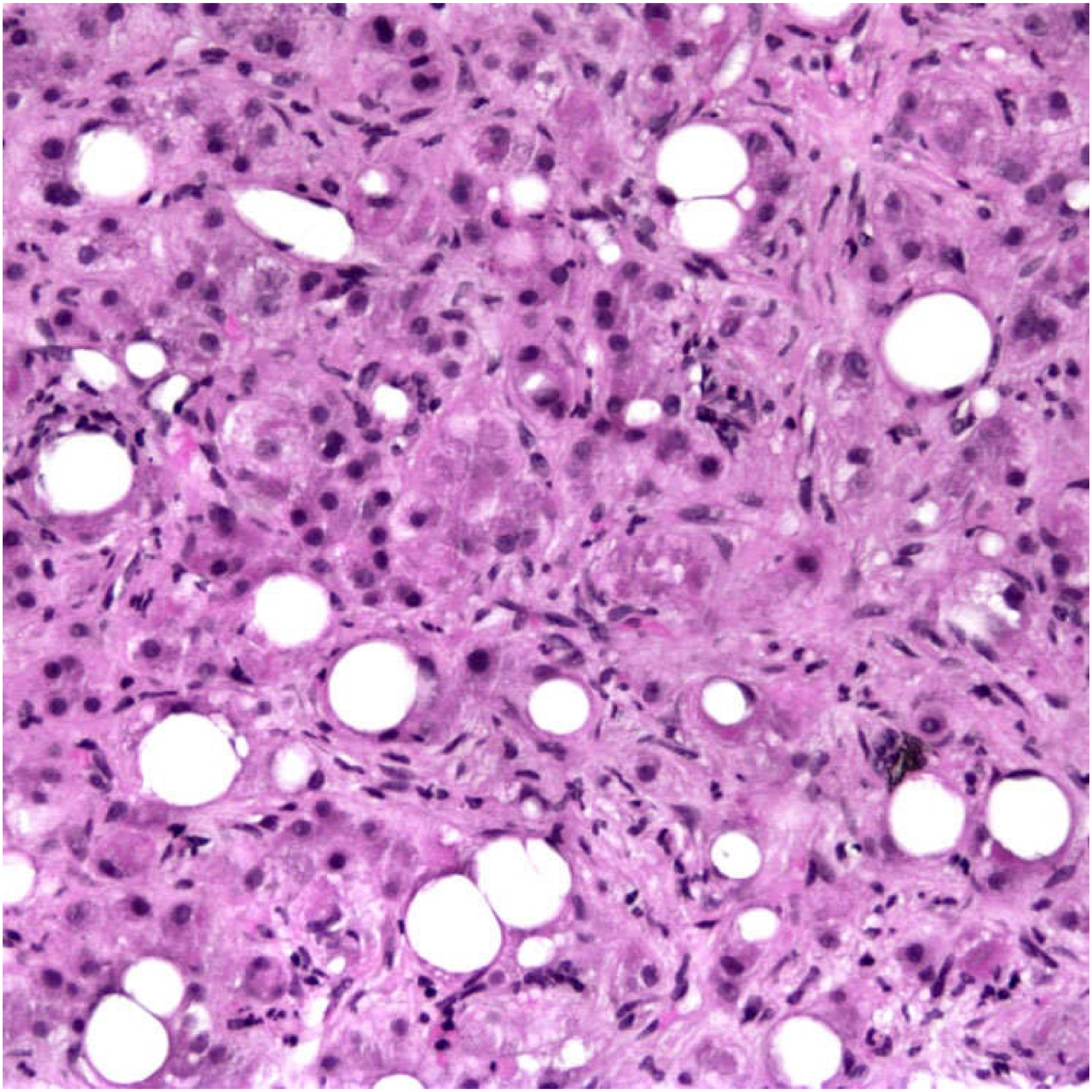


Fibrosis
As the disease progresses, pericellular fibrosis extends outward from zone 3. Note the formation of fibrous septa .

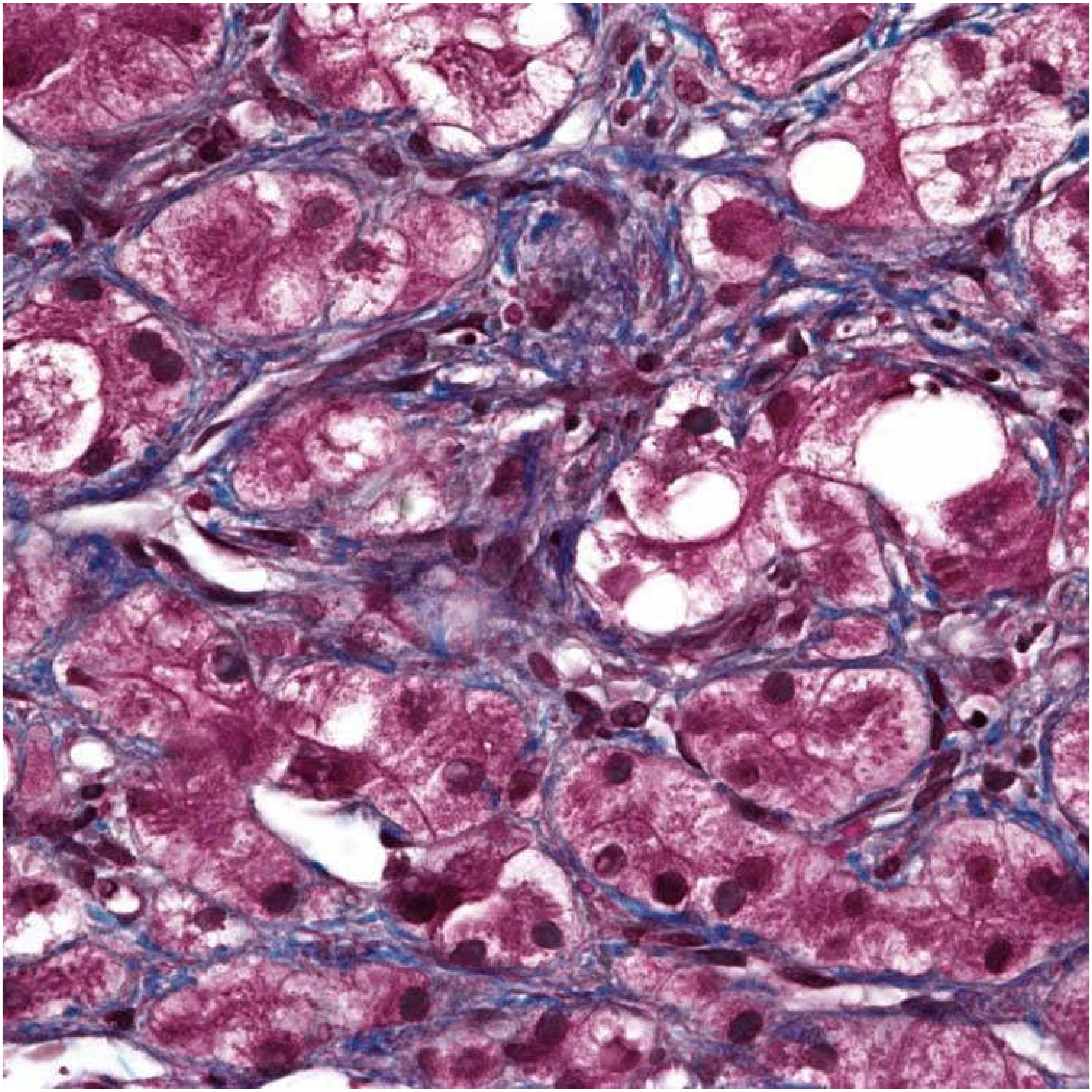


Trichrome Stain

This trichrome stain highlights multiple cirrhotic nodules in a case of end-stage liver disease. Marked steatosis is seen in this case, but significant fat may be absent in end-stage ALD, as patients must be abstinent prior to transplant.



Sclerosing Hyaline Necrosis
This case of ALD has features of sclerosing hyaline necrosis including dense pericellular fibrosis and obliteration of central veins.



Fibrosis
Dense pericellular fibrosis with compression of central veins is characteristic of sclerosing hyaline necrosis. This form of ALD can be associated with noncirrhotic portal hypertension.

SELECTED REFERENCES

1. Yeh, MM, et al. Pathological features of fatty liver disease. *Gastroenterology*. 2014; 147(4):754–764.
2. Yeh, MM, et al. Pathology of fatty liver: differential diagnosis of non-alcoholic fatty liver disease. *Diagnostic Histopathology*. 2008; 14:586–589.
3. Levitsky, J, et al. Diagnosis and therapy of alcoholic liver disease. *Semin Liver Dis*. 2004; 24(3):233–247.
4. Mandayam, S, et al. Epidemiology of alcoholic liver disease. *Semin Liver Dis*. 2004; 24(3):217–

232.
5. Brunt, EM. Alcoholic and nonalcoholic steatohepatitis. *Clin Liver Dis*. 2002; 6(2):399–420. [vii].

Nonalcoholic Steatohepatitis

KEY FACTS

Terminology

- Steatosis, inflammation, and liver cell injury in absence of history of alcohol use

Etiology/Pathogenesis

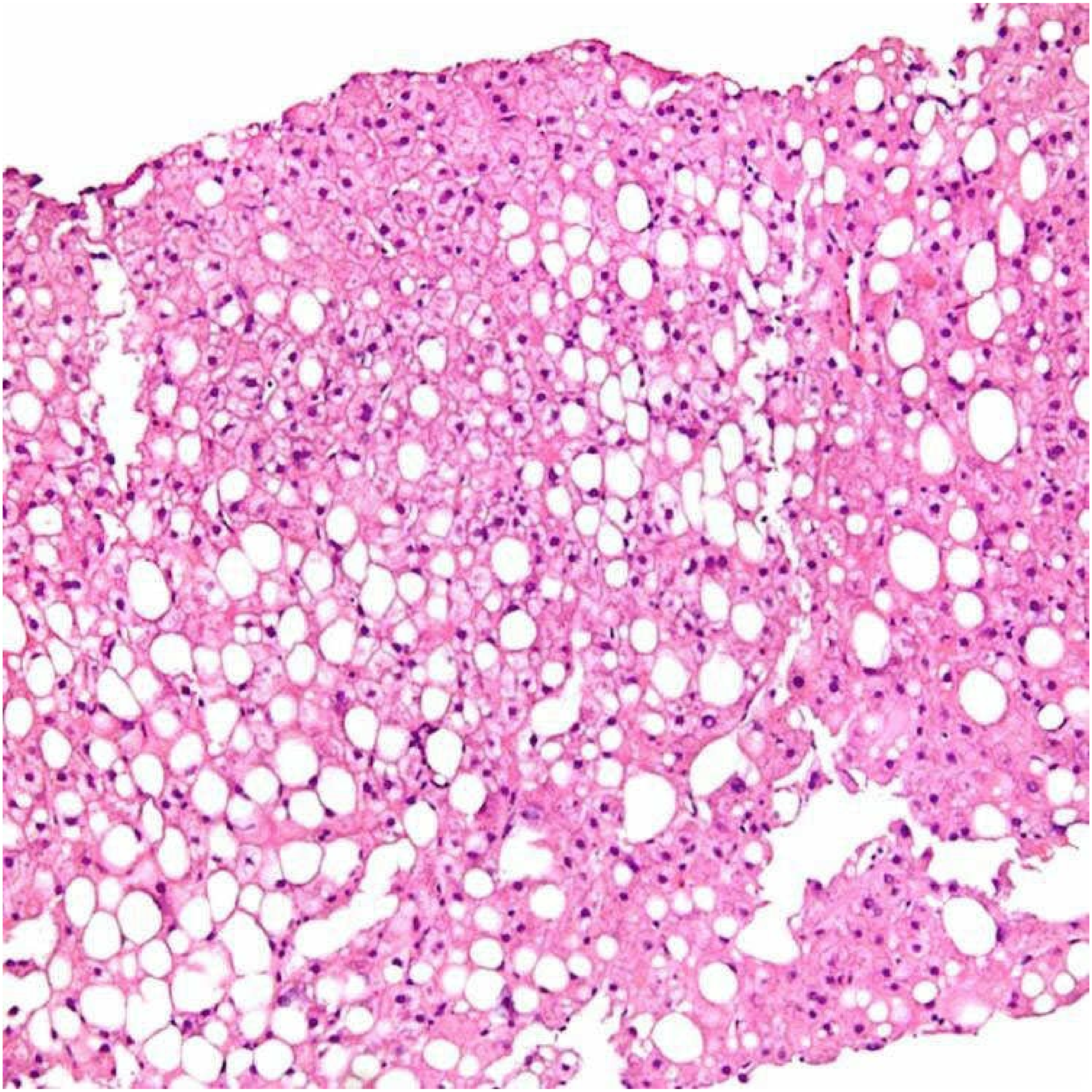
- Abnormal accumulation of lipids in hepatocytes provides source of oxidative stress and leads to injury/inflammation
- Associated conditions: Metabolic syndrome, drugs, malabsorption, malnutrition

Clinical Issues

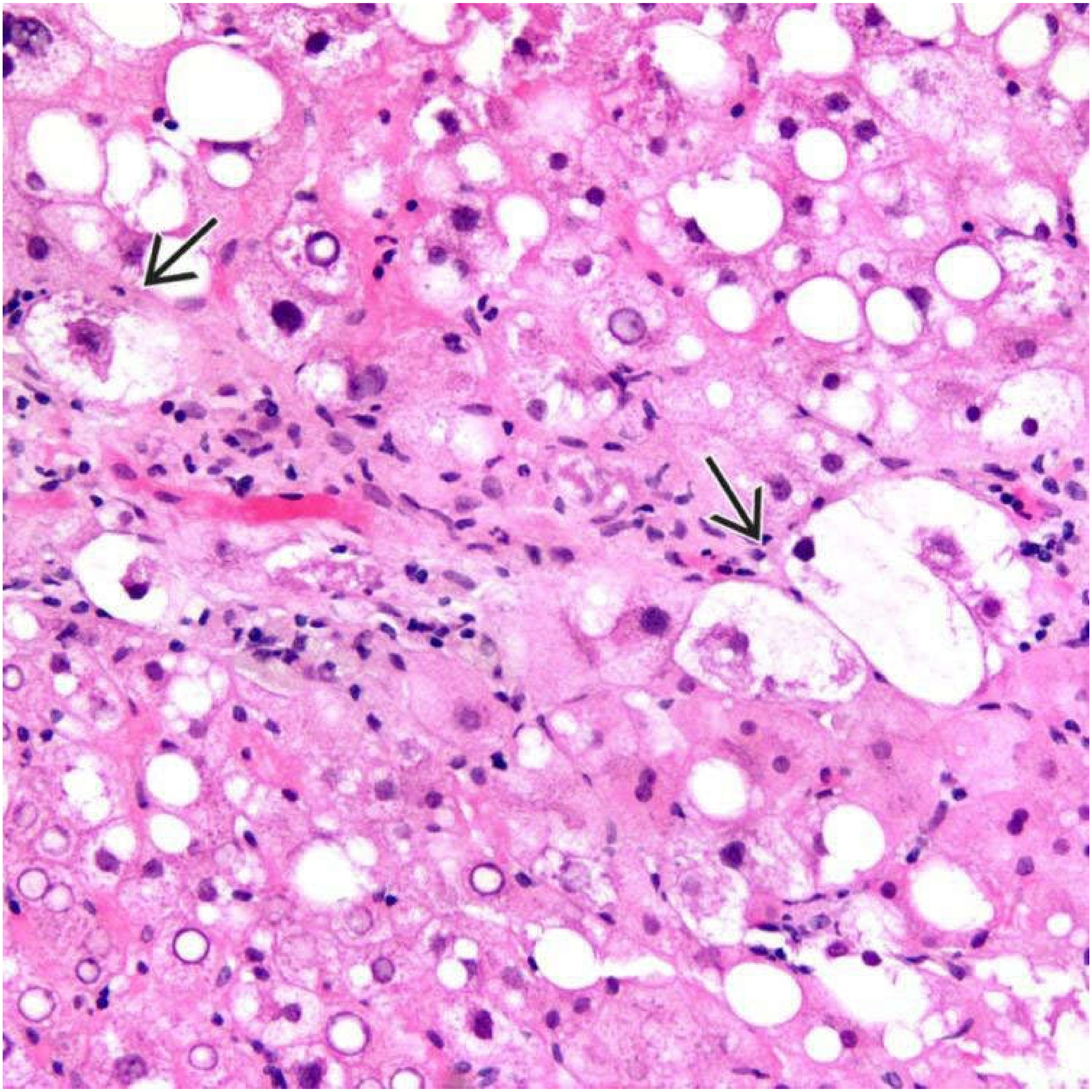
- Hepatomegaly
  - Metabolic syndrome, including central obesity, type 2 diabetes, dyslipidemia, hypertension
  - Laboratory tests
    - Elevated transaminases
- Mainstay of treatment: Management of metabolic conditions

Microscopic

- Steatosis, predominantly macrovesicular
  - Lobular inflammation (lymphocytes and Kupffer cells predominates)
  - Ballooning
  - Both fat and ballooning are most prominent in zone 3
  - Mallory-Denk bodies, megamitochondria, glycogenated nuclei
  - Fibrosis begins as zone 3 perivenular/pericellular (chicken wire) fibrosis (with exception of pediatric patients); may progress to bridging fibrosis, cirrhosis
  - If portal inflammation is accentuated, think of advanced disease or concomitant chronic liver disease
  - Nonalcoholic steatohepatitis in pediatric population has different injury pattern
    - Inflammation, fibrosis accentuated in portal region
    - Ballooning degeneration and perisinusoidal fibrosis not obvious

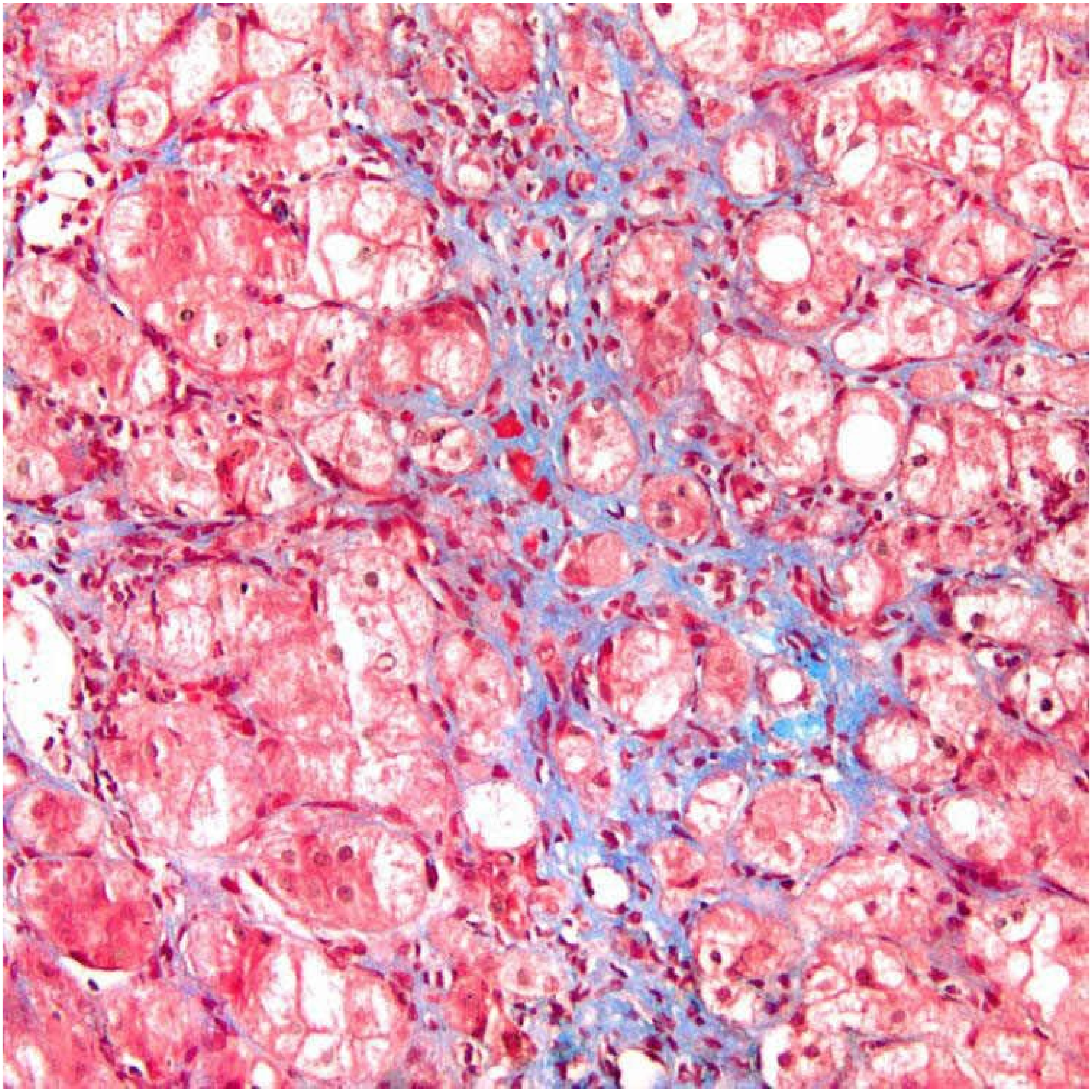


Macrovesicular Steatosis
Macrovesicular steatosis is common in nonalcoholic steatohepatitis (NASH). It frequently begins in zone 3, particularly in adults, and may extend to become panzonal.

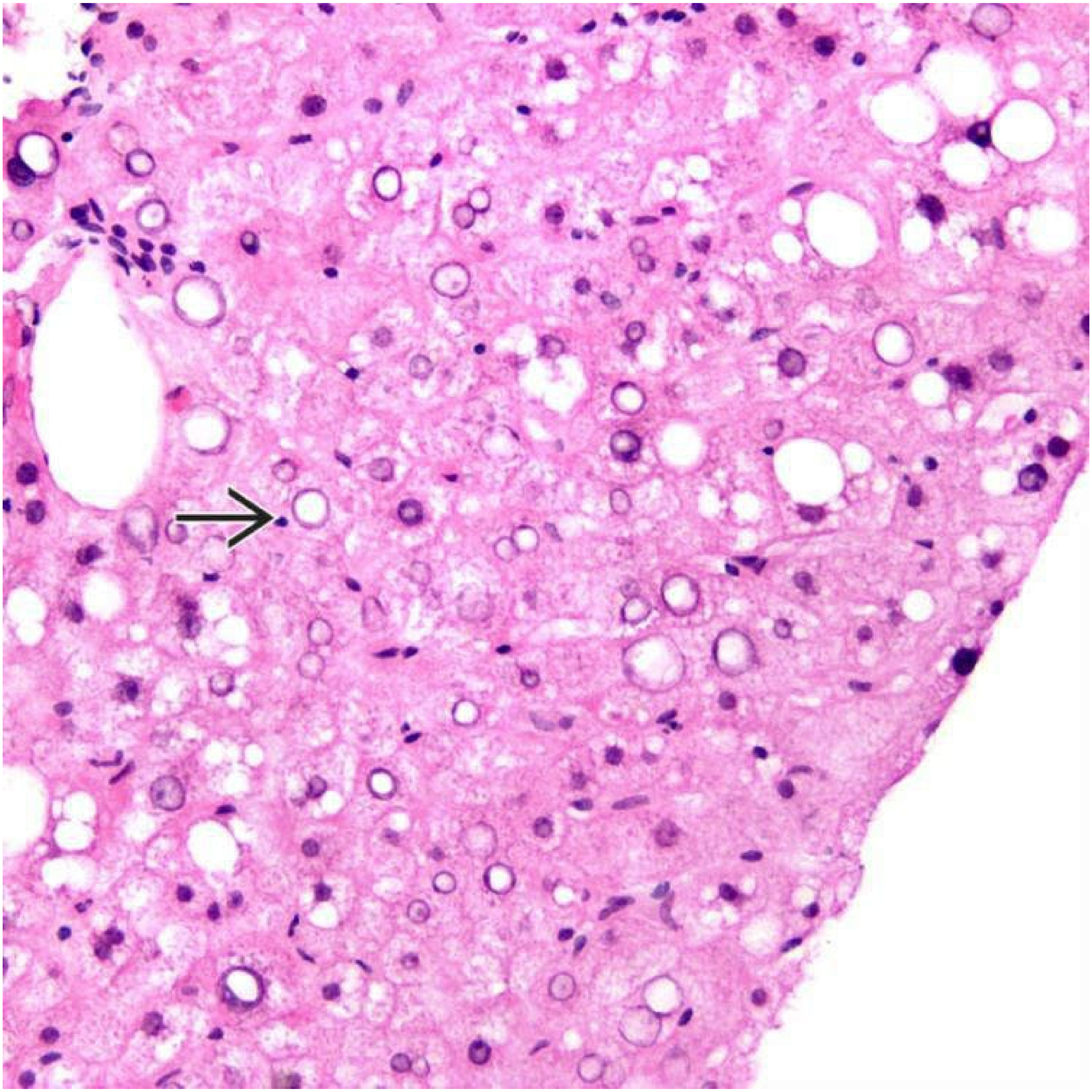


Hepatocyte Ballooning

Ballooned hepatocytes → are common in NASH and may be associated with Mallory-Denk bodies. Note the steatosis and glycogenated nuclei as well.



Pericellular Fibrosis
Trichrome stain highlights the pericellular fibrosis that is typical of steatohepatitis and NASH. In adults, the fibrosis typically begins in zone 3.



Glycogenated Nuclei
Glycogenated nuclei →, featuring clear, vesicular nuclei within hepatocytes, are a common, but nonspecific, finding in NASH.

TERMINOLOGY

Abbreviations

- Nonalcoholic steatohepatitis (NASH)

Definitions

- Steatosis, inflammation, and ballooning in absence of history of alcohol use

ETIOLOGY/PATHOGENESIS

Mechanism

- Hepatic accumulation of lipids provides source of oxidative stress and leads to injury/inflammation
- Subsequent activation of TGF-β and hepatic stellate cells results in fibrosis

Associated Conditions

- Metabolic syndrome, drugs, malabsorption, malnutrition

CLINICAL ISSUES

Presentation

- Hepatomegaly
- Metabolic syndrome, including central obesity, type 2 diabetes, dyslipidemia, hypertension

Laboratory Tests

- Elevated transaminases

Treatment

- Management of associated metabolic syndrome
- Many drugs under investigation

Prognosis

- May progress to fibrosis, cirrhosis, and hepatocellular carcinoma

MICROSCOPIC

Histologic Features

- Steatosis, predominantly macrovesicular
  - Lobular inflammation (lymphocytes and Kupffer cells predominates)
  - Liver cell injury: Ballooning of hepatocytes, apoptotic bodies
  - Both fat and ballooning are most prominent in zone 3
  - Mallory-Denk bodies, megamitochondria, glycogenated nuclei
  - Fibrosis
  - Begins as zone 3 pericentral (chicken wire) fibrosis, with exception of pediatric patients
  - May progress to bridging, cirrhosis
- If portal inflammation is accentuated, think of advanced disease or concomitant chronic liver disease

Variants

- Pediatric patients
  - Inflammation and fibrosis accentuated in portal (not centrilobular) region
  - Ballooning degeneration and pericentral fibrosis typically much less obvious

Grading and Staging

- 2 major schemes that grade activity and stage fibrosis
  - Brunt scheme
  - Nonalcoholic fatty liver disease activity and fibrosis scoring from NASH Clinical Research Network

DIFFERENTIAL DIAGNOSIS

Steatosis (Without Specific Liver Injury)

- Lack of ballooned hepatocytes

Alcoholic Hepatitis

- Almost impossible to distinguish histologically; clinical history critical
- More abundant Mallory-Denk bodies, neutrophilic aggregates in lobules

Chronic Hepatitis C

- HCV(+) antibody and RNA
- Portal-based inflammation and fibrosis; steatosis generally nonzonal

Glycogenic Hepatopathy

- Swollen hepatocytes may mimic ballooned hepatocytes

Microvesicular Steatosis

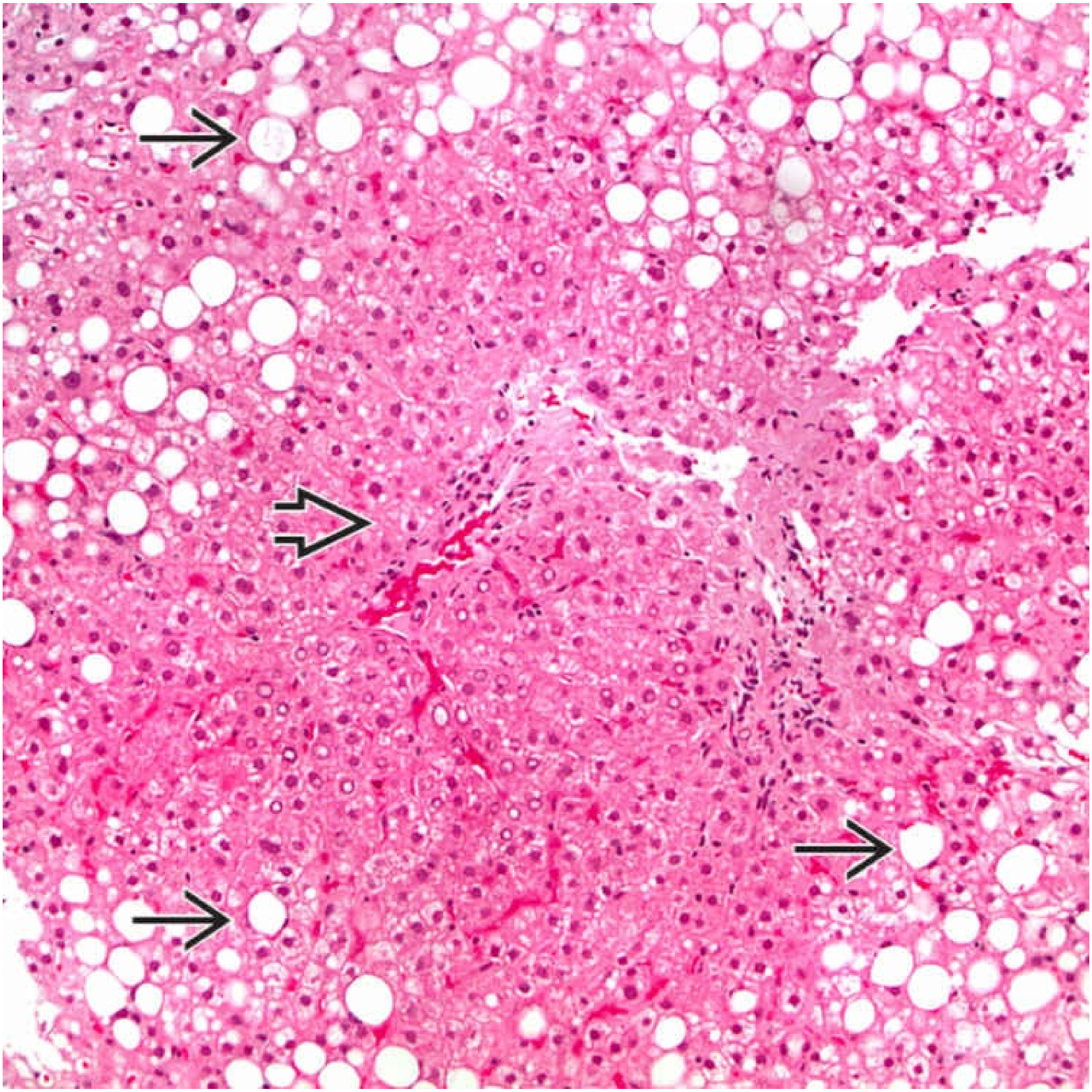
- May mimic ballooning; nuclei centrally located

Wilson Disease

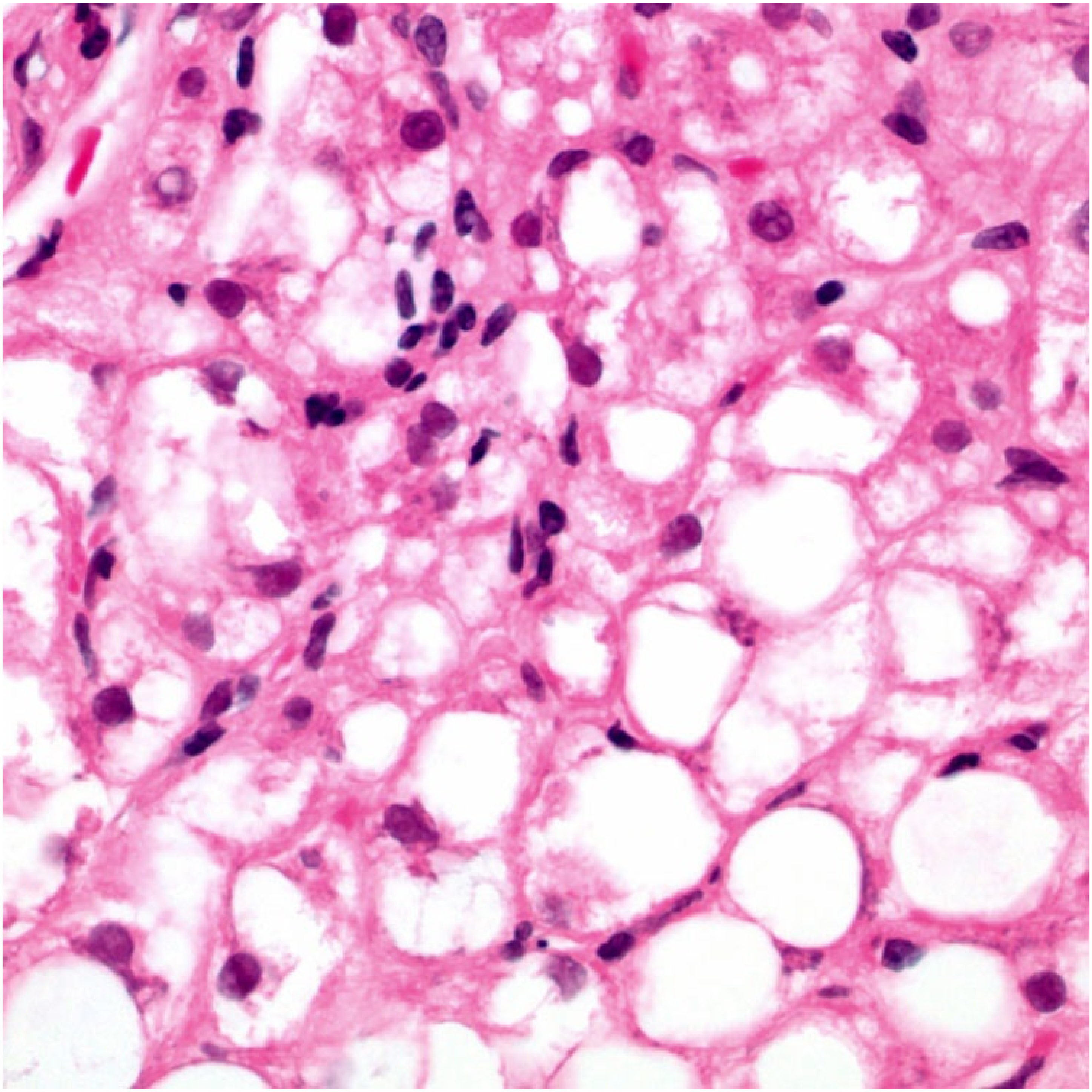
- Copper accumulation; steatosis and ballooning, may also be seen

Comparison of Adult and Pediatric Nonalcoholic Steatohepatitis

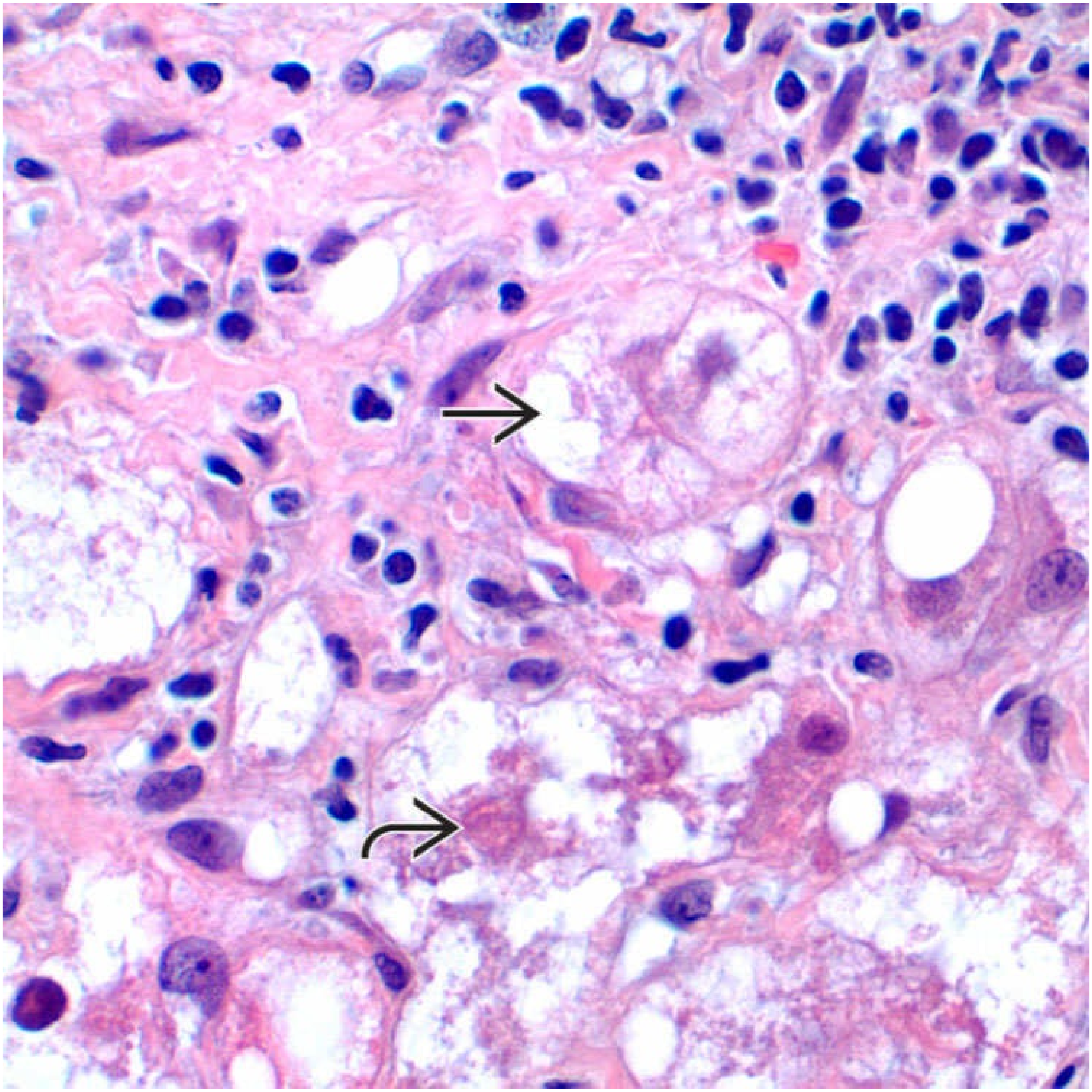
Adult Nonalcoholic Steatohepatitis	Pediatric Nonalcoholic Steatohepatitis
Zone 3 pattern of fat and inflammation	Zone 1 pattern of fat and inflammation
Fibrosis initiates from zone 3	Fibrosis initiates from zone 1
Ballooned hepatocytes are present	Lack of ballooned hepatocytes



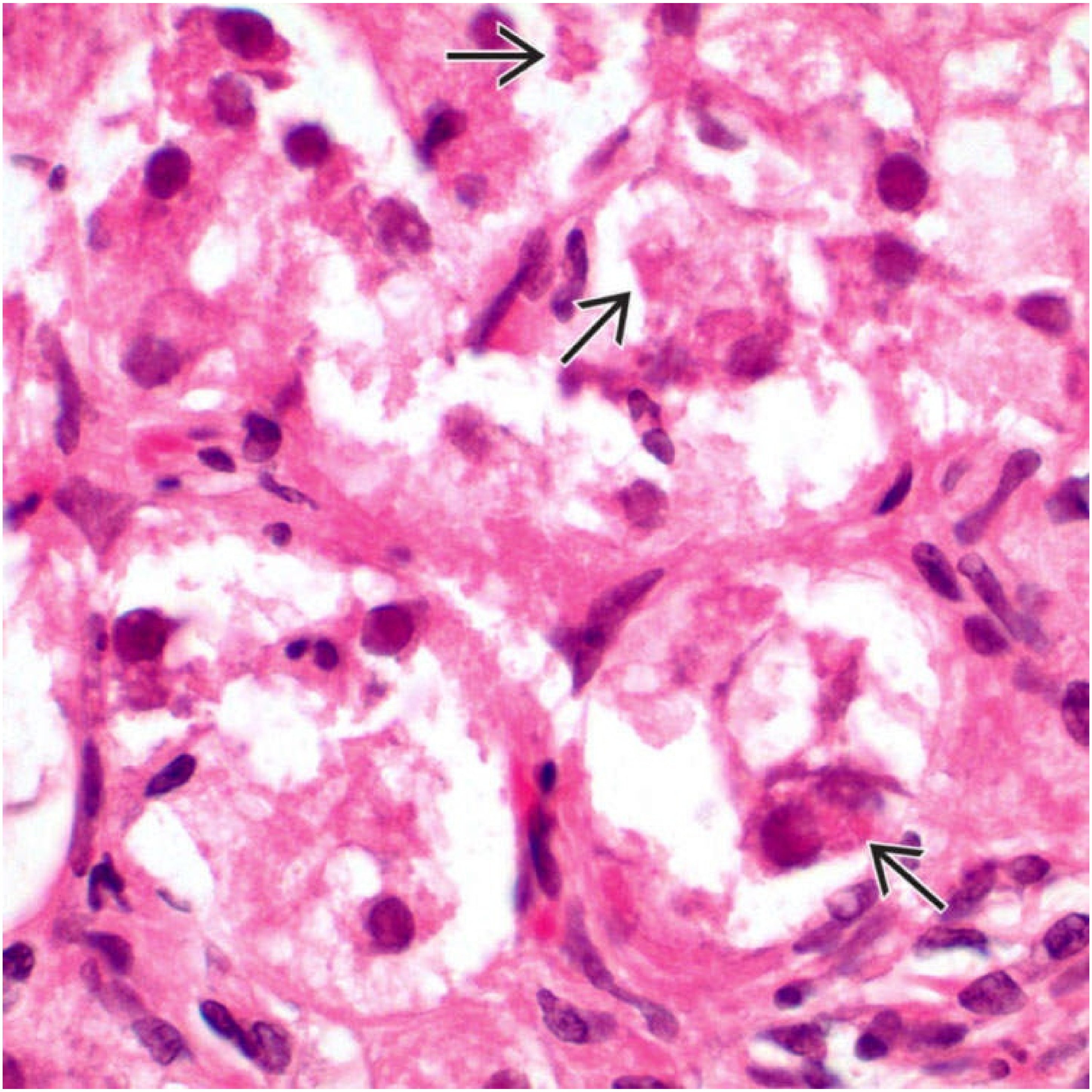
Zone 3 Steatosis
Steatosis accentuated in zone 3 → with sparing in the portal region ⇨ is a typical pattern of NASH in adults.



Lobular Inflammation
Mild lobular inflammation that is predominantly mononuclear is often seen in NASH.

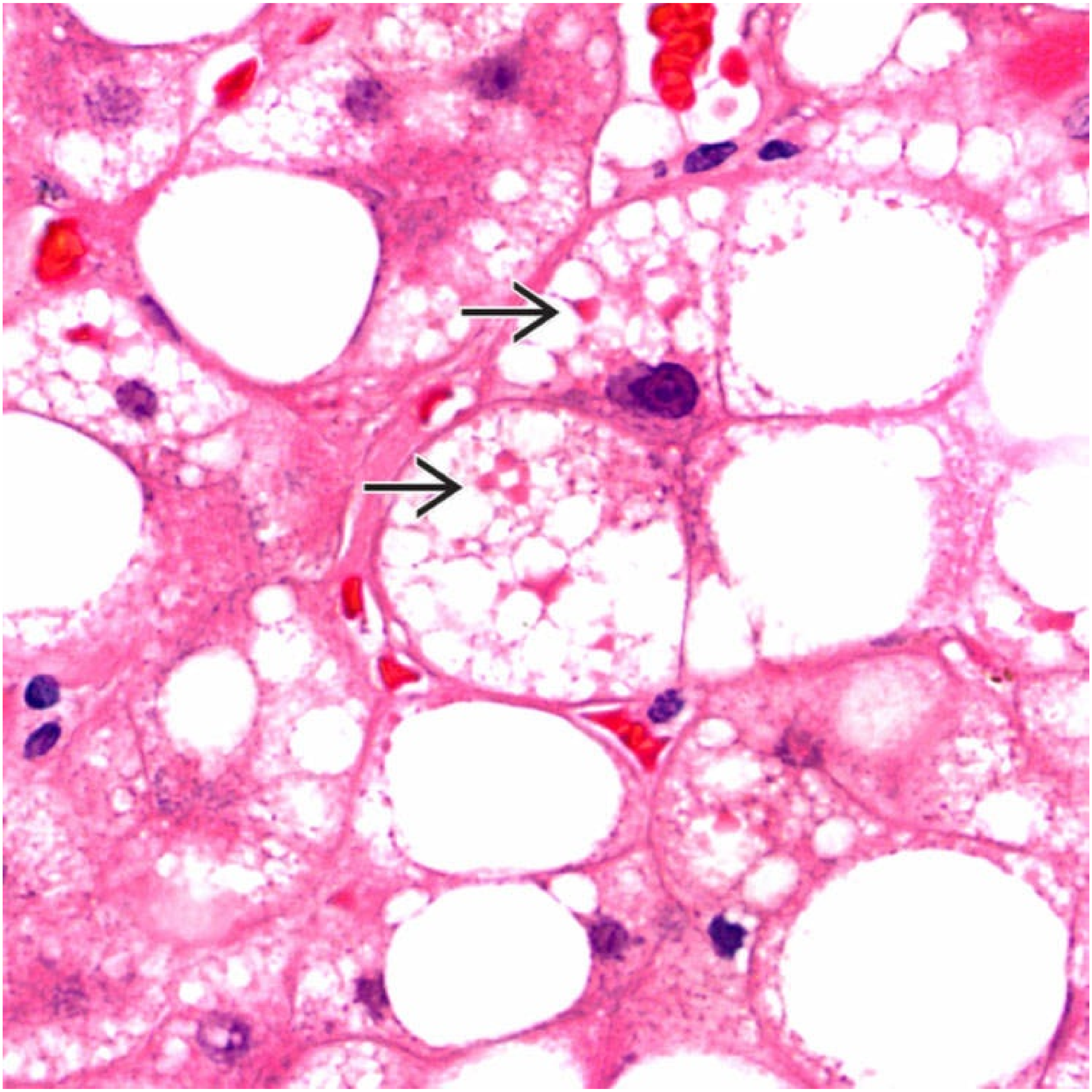


Hepatocyte Ballooning
Ballooned hepatocytes → are swollen and enlarged with rarefied and clumped cytoplasm. They sometimes contain Mallory-Denk bodies ↱ .



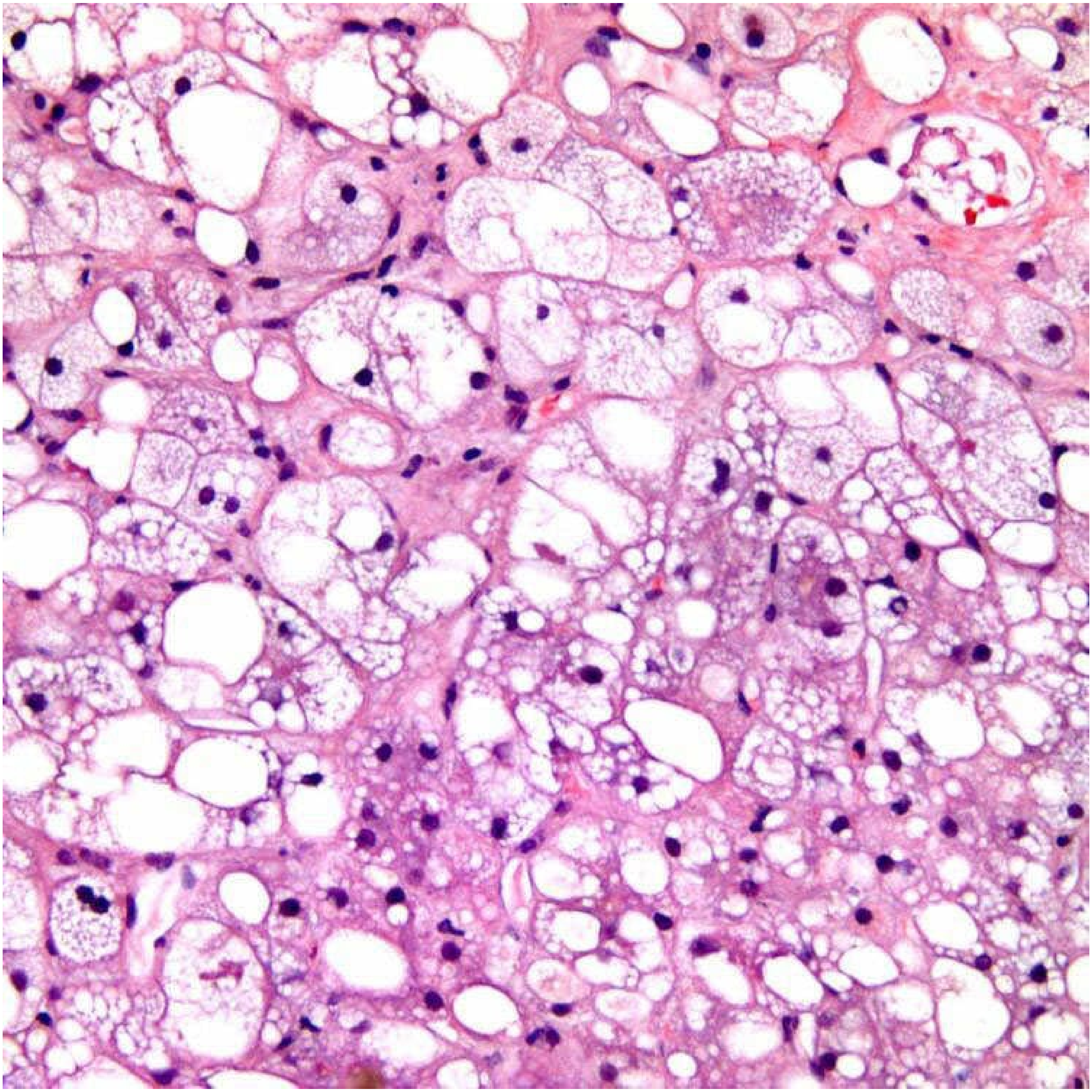
Mallory-Denk Bodies

Mallory-Denk bodies → consist of eosinophilic, ropy, &/or globular material within ballooned hepatocytes and are commonly seen in NASH as well as alcohol associated steatohepatitis.

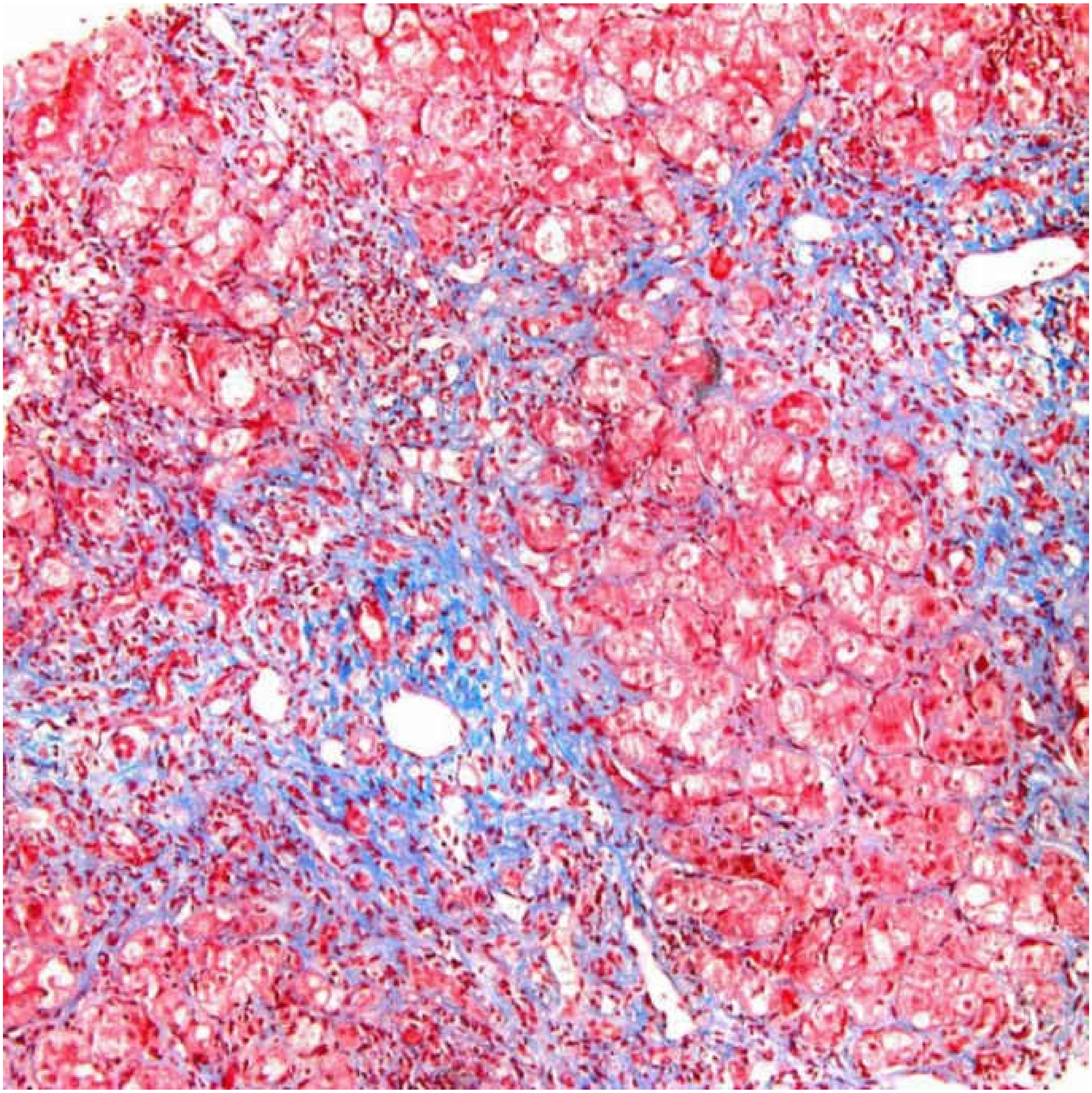


Megamitochondria

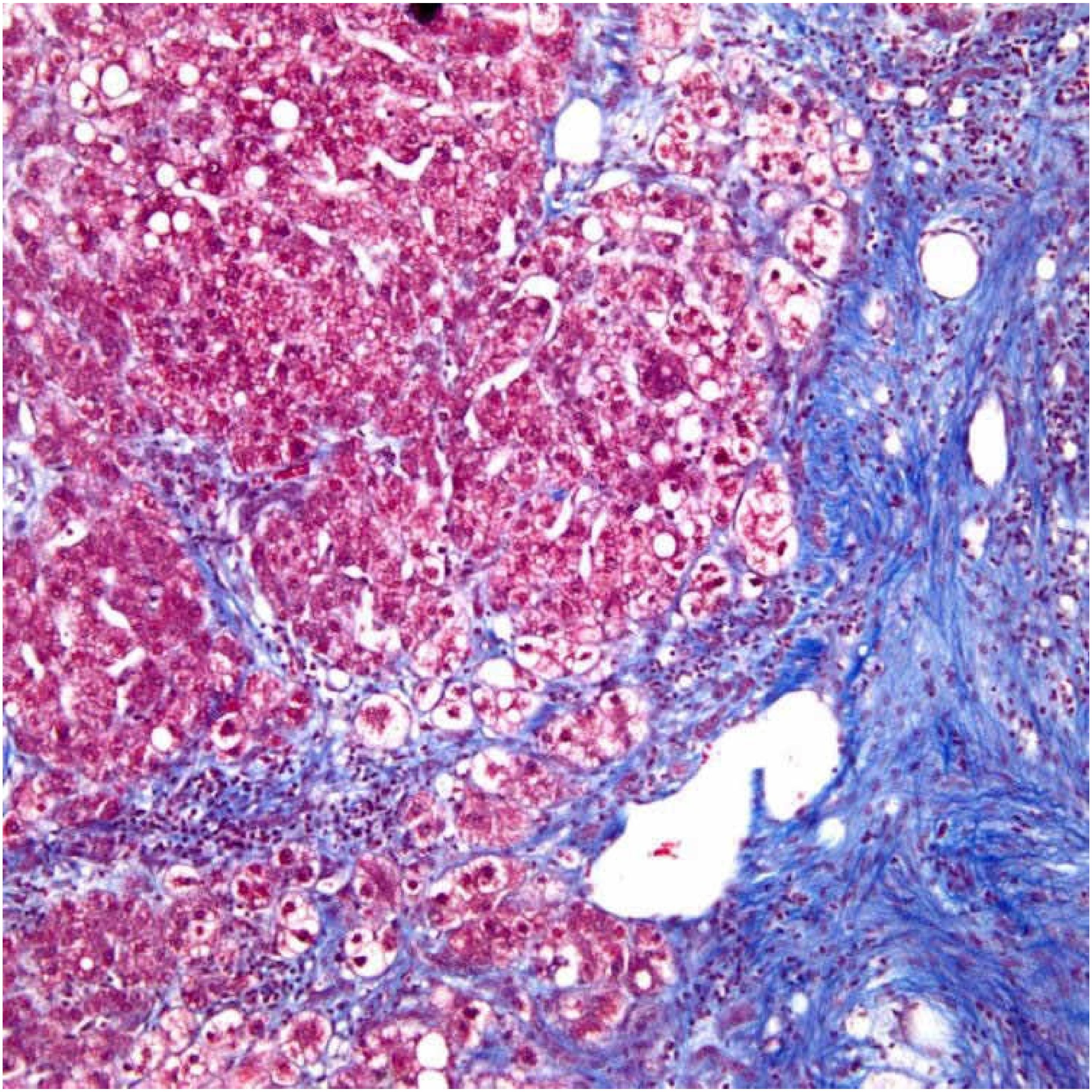
Megamitochondria (i.e., “giant” mitochondria →) are often seen in NASH and consist of intracytoplasmic oblong, round, and eosinophilic inclusions.



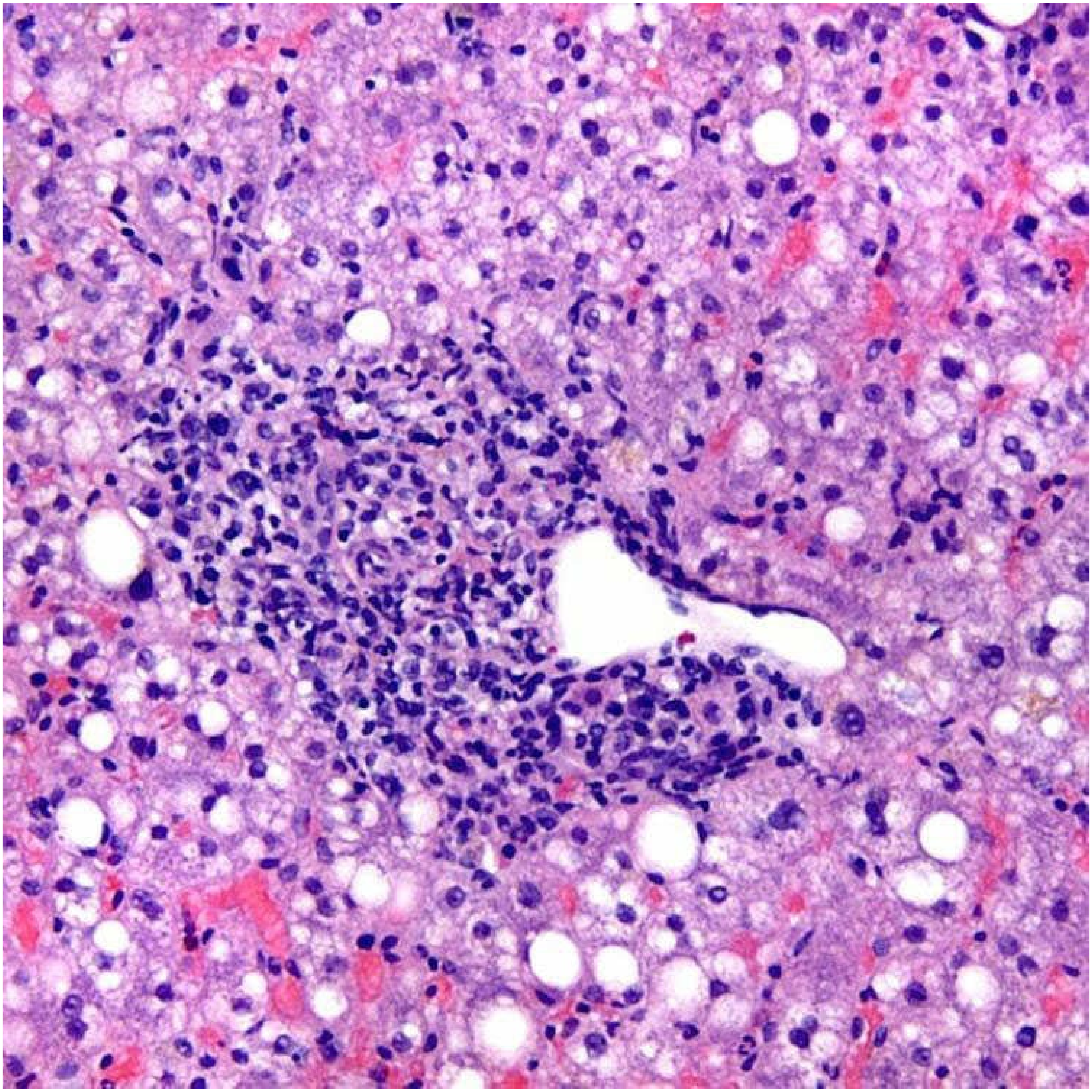
Mixed Micro- and Macrovesicular Steatosis
Sometimes the steatosis in NASH is mixed micro- and macrovesicular.



Bridging Fibrosis
This case of NASH shows both pericellular/perivenular fibrosis and periportal fibrosis, along with bridging.

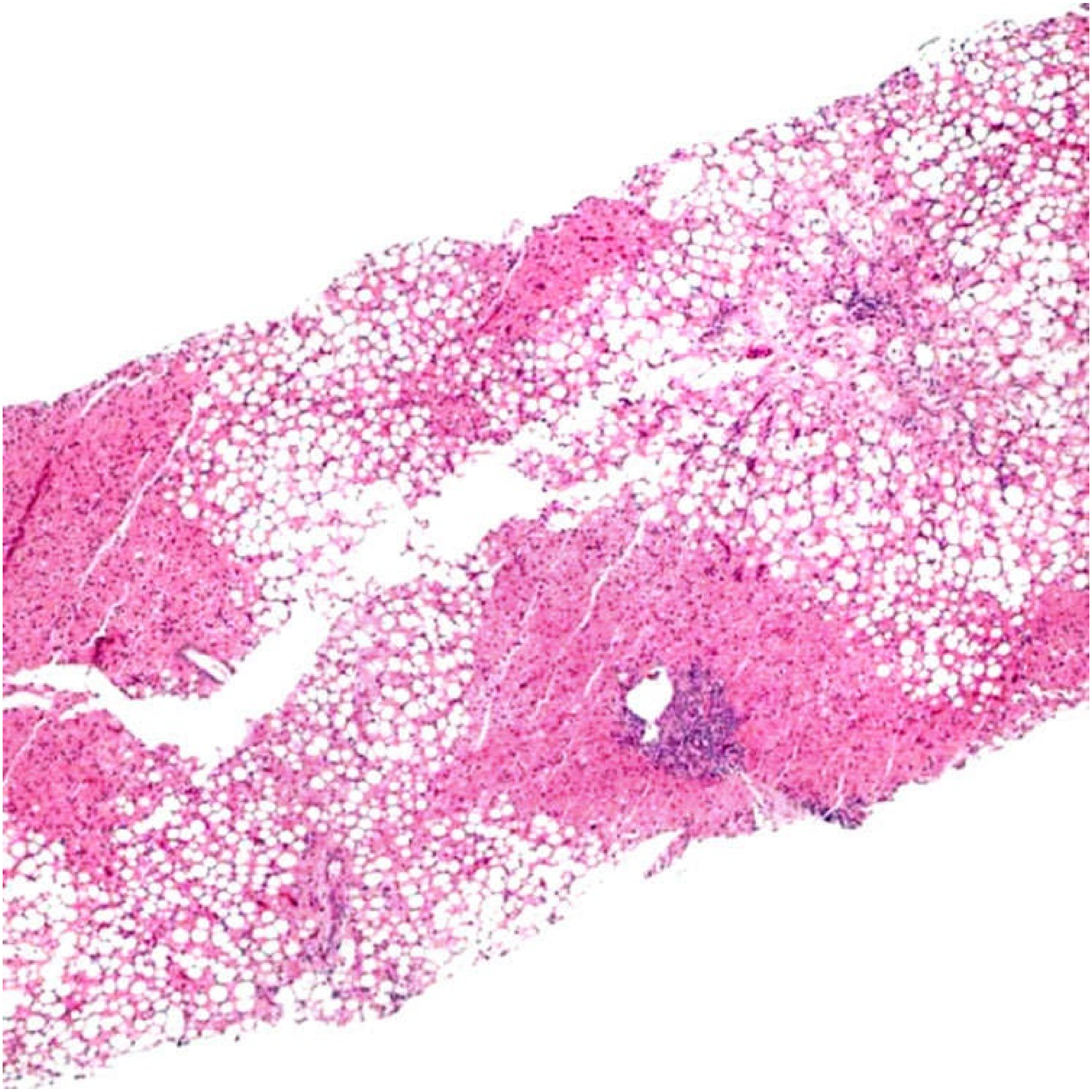


Cirrhosis
Cirrhosis secondary to NASH shows rounded nodules with hepatocyte ballooning, steatosis, and focal pericellular fibrosis.



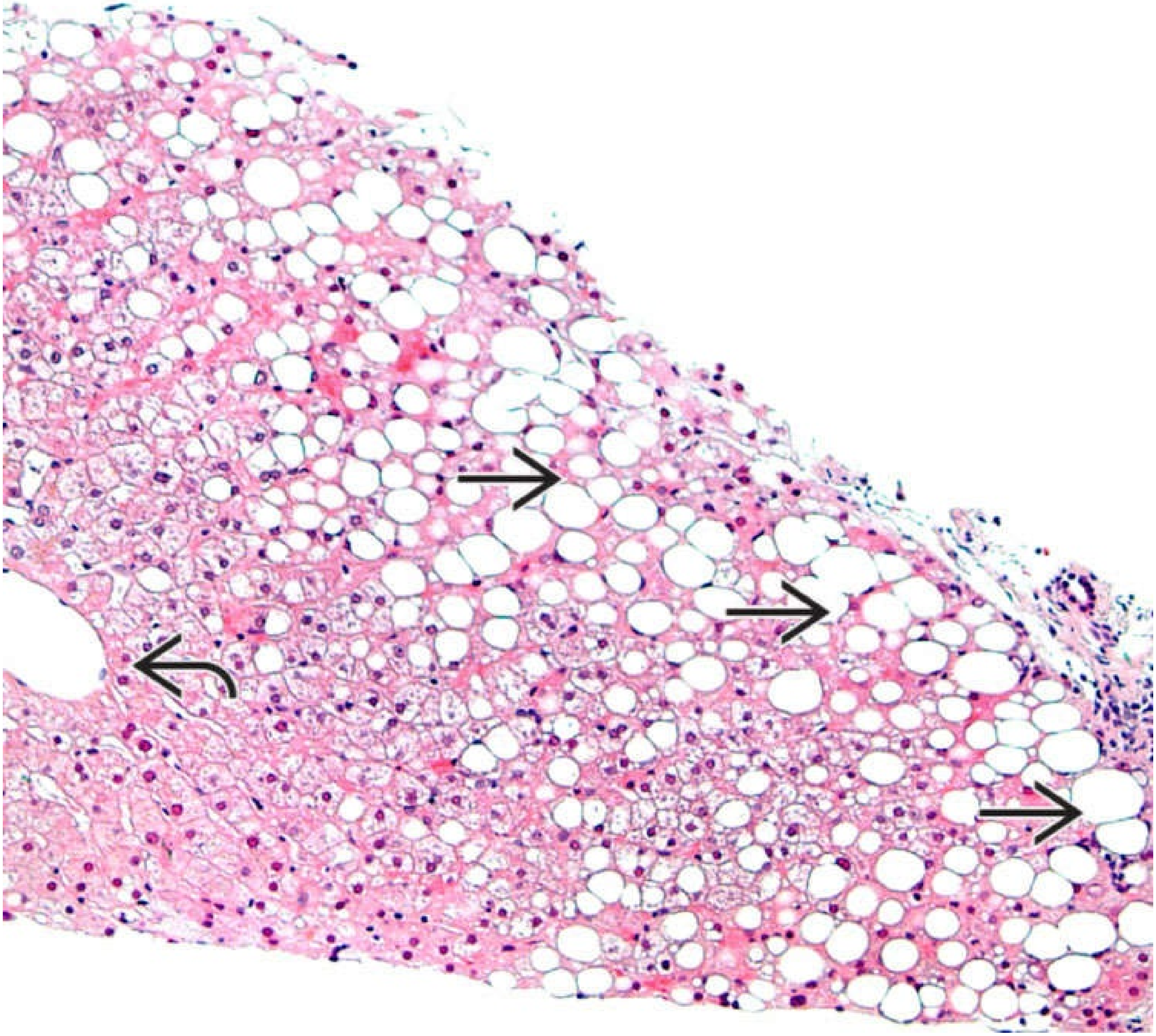
Portal Inflammation

The portal inflammation in NASH is typically fairly sparse. When there is more prominent portal inflammation, additional or alternative diagnoses should be considered, such as hepatitis C.

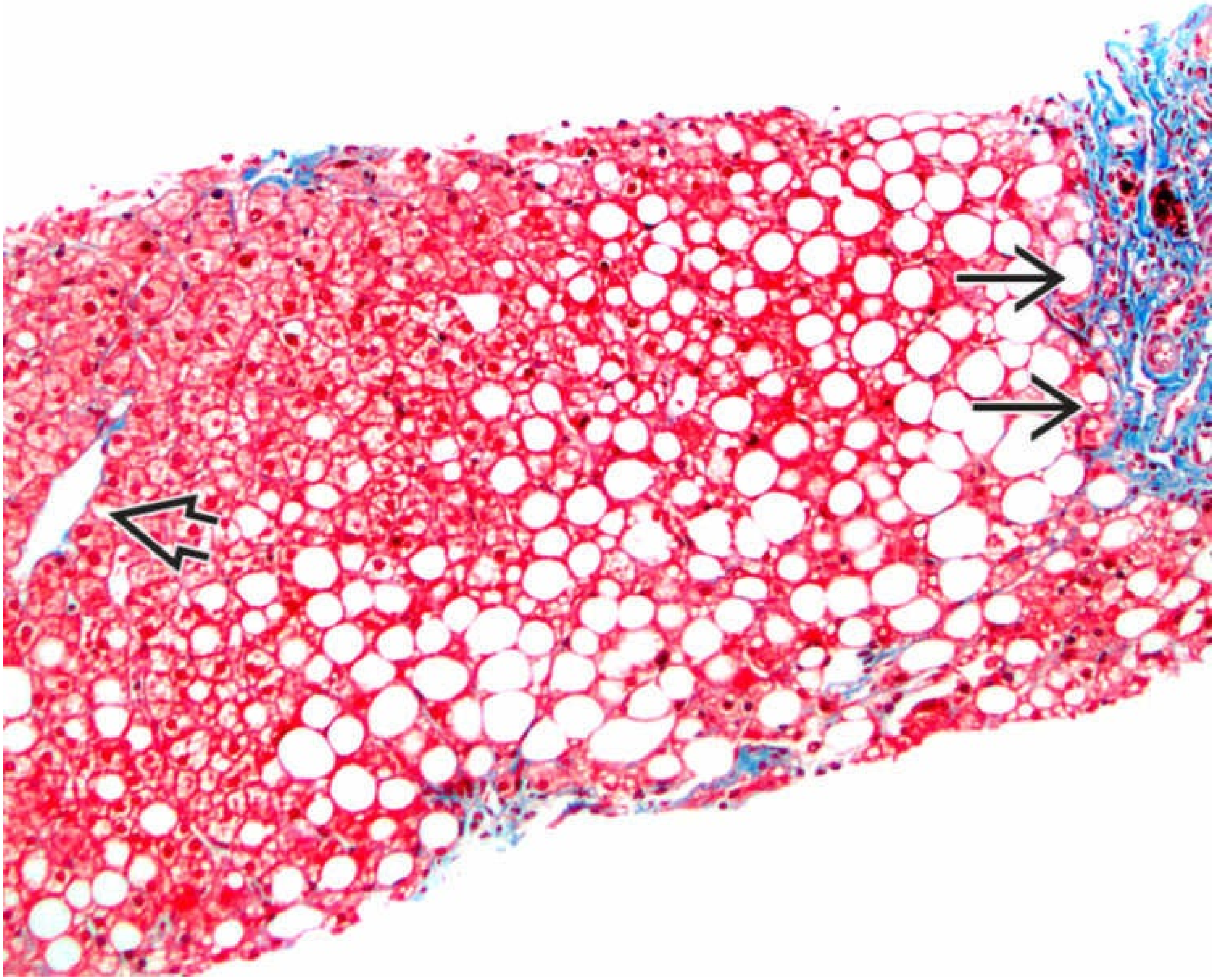


Hepatitis C

A case of concomitant NASH and chronic hepatitis C shows zone 3 steatosis and hepatocyte injury, along with dense chronic portal inflammation and lymphoid aggregates typical of hepatitis C.



Pediatric Patients
Unlike adults, the steatosis of NASH in pediatric patients is typically accentuated in zone 1 →, with sparing of zone 3 ↷.



Pediatric Patients

NASH in pediatric patients is typically characterized by portal-based fibrosis → rather than zone 3 pericellular fibrosis. Note the unremarkable hepatic vein without surrounding fibrosis ⇨ .

SELECTED REFERENCES

1. Tilg, H, et al. Evolving therapies for non-alcoholic steatohepatitis. *Expert Opin Drug Discov*. 2014; 9(6):687–696.
2. Yeh, MM, et al. Pathological features of fatty liver disease. *Gastroenterology*. 2014; 147(4):754–764.
3. Yeh, MM, et al. Pathology of nonalcoholic fatty liver disease. *Am J Clin Pathol*. 2007; 128(5):837–847.
4. Kleiner, DE, et al. Design and validation of a histological scoring system for nonalcoholic fatty

liver disease. *Hepatology*. 2005; 41(6):1313–1321.
6. Brunt, EM, et al. Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. *Am J Gastroenterol*. 1999; 94(9):2467–2474.

5. Schwimmer, JB, et al. Histopathology of pediatric nonalcoholic fatty liver disease. *Hepatology*. 2005; 42(3):641–649.

Glycogenic Hepatopathy

KEY FACTS

Terminology

- Hepatomegaly and elevated liver enzymes associated with poorly controlled diabetes mellitus and abundant glycogen in hepatocytes

Etiology/Pathogenesis

- Chronic hyperglycemia due to poorly controlled insulin-dependent diabetes mellitus
- Longstanding high blood sugar levels lead to glycogen accumulation in hepatocytes
- Hepatomegaly and transaminase elevations attributed to this excess glycogen accumulation

Clinical Issues

- Abdominal pain
- Elevated transaminases
- Hepatomegaly
- Occurs in patients with history of poorly controlled insulin-dependent diabetes mellitus
- Liver histology improves and transaminases normalize with optimization of glycemic control

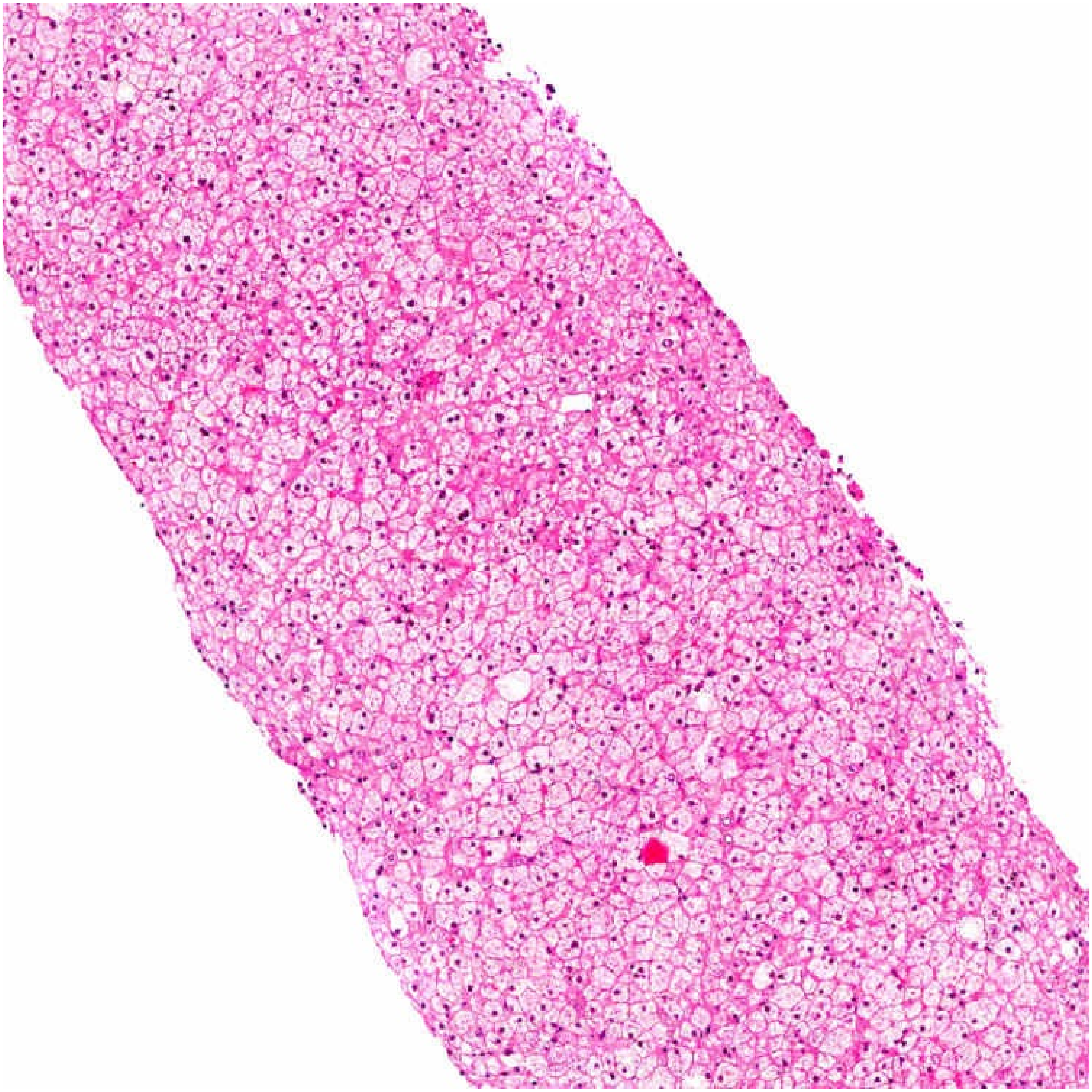
Microscopic

- Diffuse, pale-staining hepatocytes
- Excessive glycogen storage in hepatocytes demonstrated by PAS stain
- Absence of inflammation or evidence of other liver disease

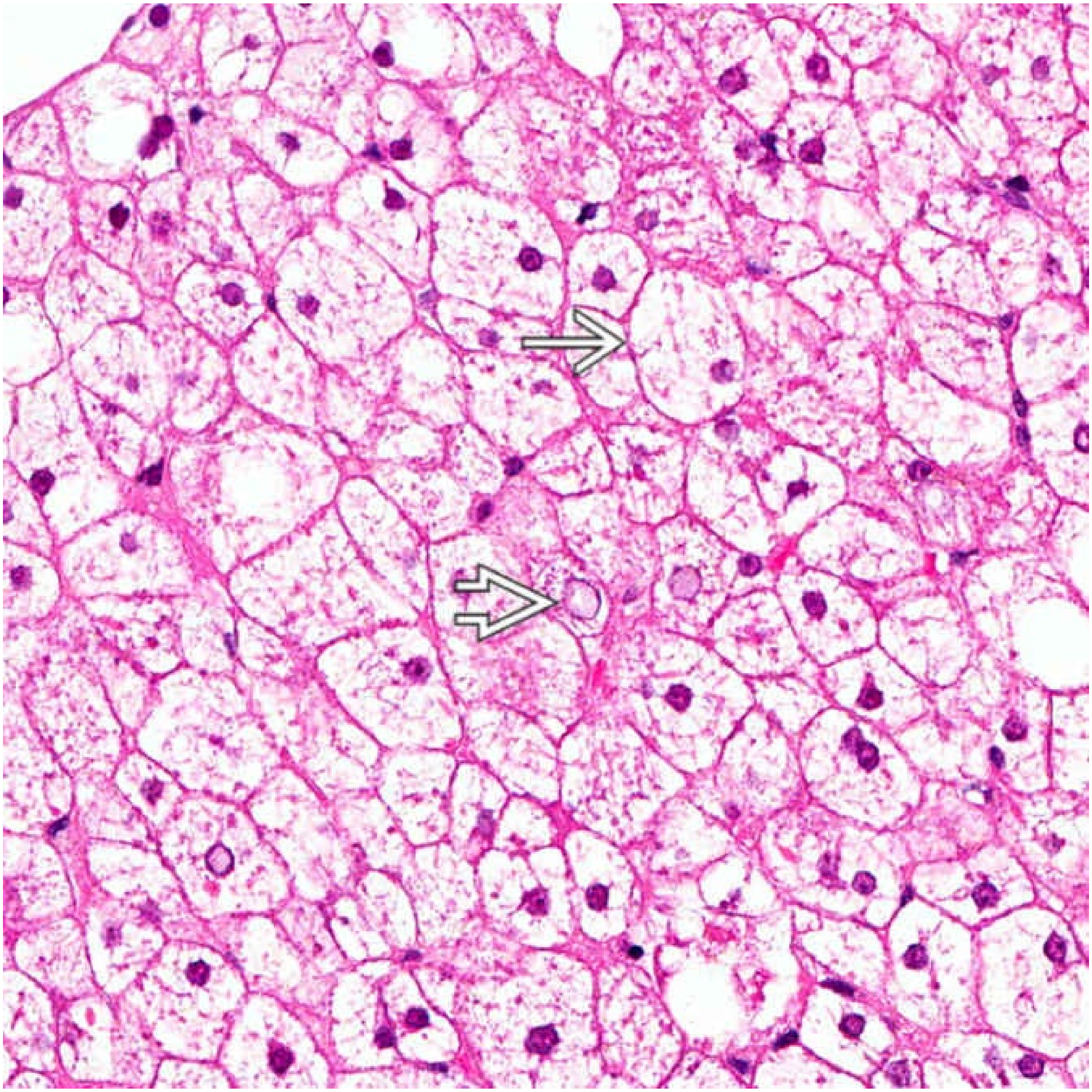
Top Differential Diagnoses

- Normal liver
  - Pale, enlarged hepatocytes may be mistaken for normal or interpreted as fixation artifact
- Fatty liver disease
  - Pale, enlarged hepatocytes may be misinterpreted as ballooning hepatocyte degeneration

- Glycogen storage disease
  - No history of diabetes mellitus

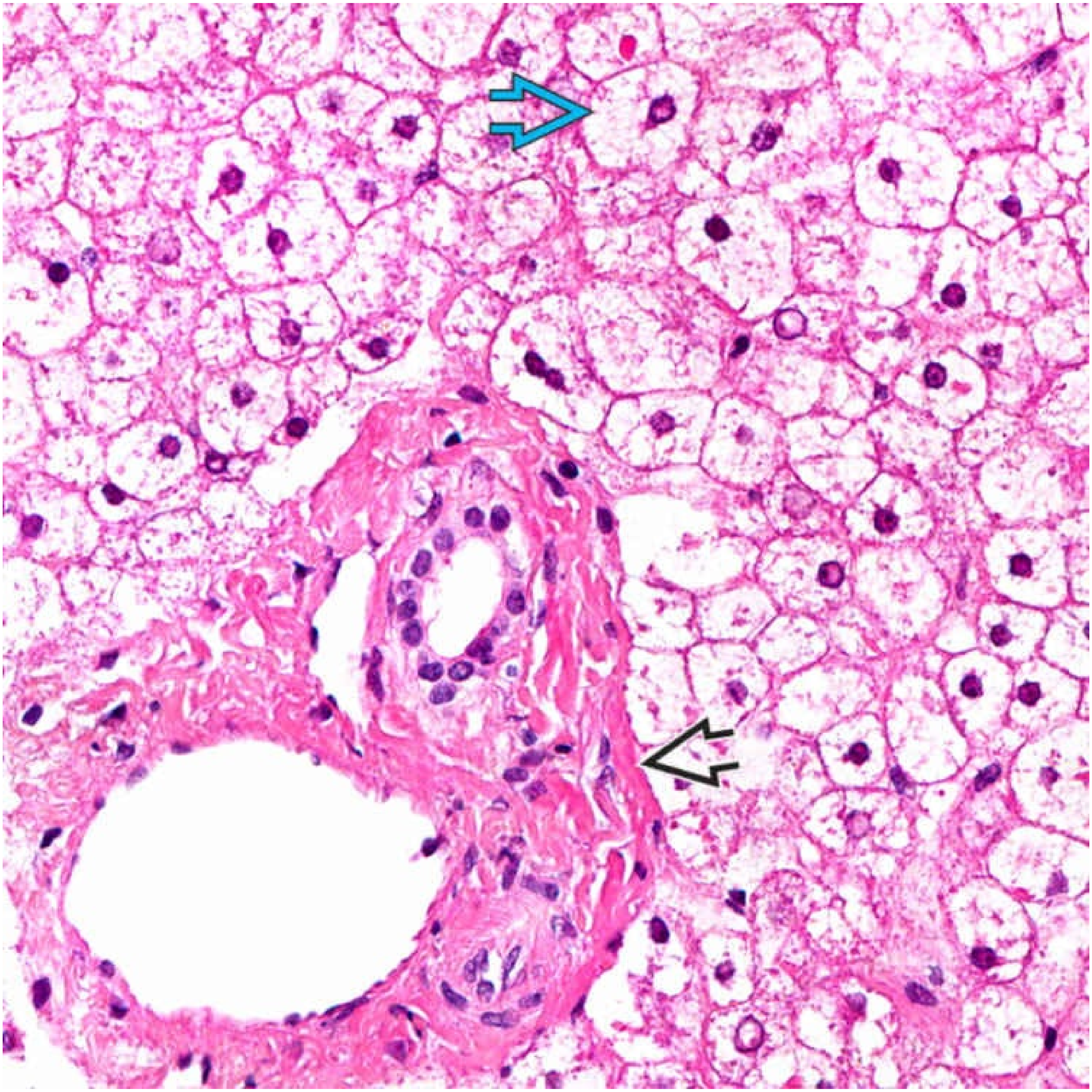


Pale Swollen Hepatocytes Without Inflammation
Needle biopsy of the liver shows diffuse hepatocyte swelling, imparting an overall pale appearance. Steatotic vacuoles are absent or rare. There is no lobular inflammation.



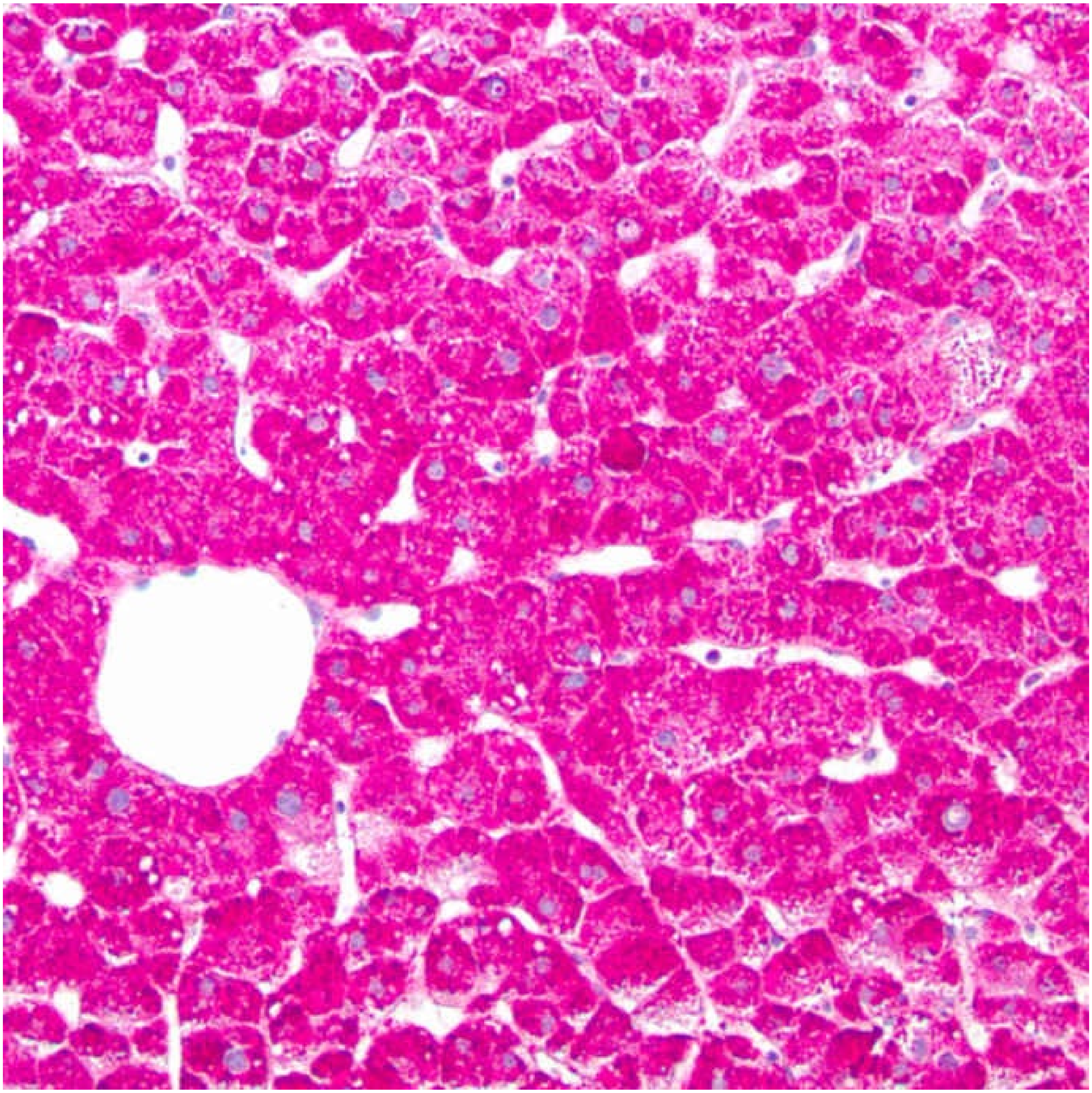
Cytologic Features

Liver biopsy from a patient with glycogenic hepatopathy shows diffuse enlargement of hepatocytes with pale, wispy cytoplasm and prominent cytoplasmic membranes . Glycogenated hepatocyte nuclei are common.



Sparing of Portal Tracts

The portal tracts appear normal in glycogenic hepatopathy. They contain their normal structures, and there are no portal inflammatory cell infiltrates. The background hepatocytes are diffusely swollen and filled with glycogen.



Hepatocytes: PAS Stain
PAS stain highlights the abundant glycogen in hepatocytes in a liver biopsy from a patient with glycogenic hepatopathy.

TERMINOLOGY

Synonyms

- Hepatic glycogenosis
  - Liver glycogenosis
  - Glycogen hepatopathy
  - Diabetes mellitus-associated glycogen storage hepatomegaly
  - Mauriac syndrome
    - Liver changes accompanied by growth retardation, delayed puberty, hypercholesterolemia, and cushingoid features

Definitions

- Excessive glycogen storage in hepatocytes secondary to poorly controlled insulin-dependent diabetes mellitus

ETIOLOGY/PATHOGENESIS

Metabolic Factors

- Chronic hyperglycemia due to poorly controlled insulin-dependent diabetes mellitus
- Longstanding high blood sugar levels lead to glycogen accumulation in hepatocytes
- Hepatomegaly and transaminase elevations attributed to this excess glycogen accumulation

CLINICAL ISSUES

Epidemiology

- Age
  - Occurs in both children and adults

Presentation

- Abdominal pain
- Hepatomegaly
- Nausea
- Vomiting
- History of ketoacidosis

Laboratory Tests

- Hyperglycemia
- Elevated transaminases
- Alkaline phosphatase may also be elevated
- Elevated hemoglobin A1c (HbA1c) indicates history of poor glycemic control

Treatment

- Options, risks, complications
  - Mainstay treatment is improved management of diabetes mellitus
    - Optimization of glycemic control with insulin and diet
- Surgical approaches
  - Resolution after pancreas transplantation has been reported

Prognosis

- Excellent outcome with medical management

- Liver histology improves and transaminases normalize with optimization of glycemic control

IMAGING

Radiographic Findings

- Hyperdense liver on CT scan without administration of contrast material

MACROSCOPIC

General Features

- Hepatomegaly

MICROSCOPIC

Histologic Features

- Diffuse pale-staining hepatocyte cytoplasm
- PAS stain confirms excessive glycogen accumulation in hepatocytes
- Rare acidophil bodies may be seen
- Glycogenated hepatocyte nuclei
- Notable absence of inflammation or other features of hepatic injury
- Fibrosis is rare

ANCILLARY TESTS

Electron Microscopy

- Marked glycogen accumulation in hepatocyte cytoplasm and nuclei

DIFFERENTIAL DIAGNOSIS

Normal Liver

- Pale, enlarged hepatocytes may be mistaken for normal or interpreted as fixation artifact

Fatty Liver Disease

- Pale, enlarged hepatocytes may be misinterpreted as ballooning hepatocyte degeneration
- Most cases of glycogenic hepatopathy show little or no steatosis

Glycogen Storage Disease

- Typically presents at younger age and without history of diabetes mellitus

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Marked transaminase elevation attributed to excessive glycogen accumulation in hepatocytes

Pathologic Interpretation Pearls

- Consider in patients with poorly controlled diabetes mellitus and unexplained hepatomegaly &/or transaminase elevations
  - Pale, slightly swollen hepatocytes with prominent cell membranes
    - May be mistaken for normal hepatocytes, glycogen storage disease, or fixation artifact

SELECTED REFERENCES

1. Sweetser, S, et al. The bright liver of glycogenic hepatopathy. *Hepatology*. 2010; 51(2):711–712.
2. Fridell, JA, et al. Complete reversal of glycogen hepatopathy with pancreas transplantation: two cases. *Transplantation*. 2007; 83(1):84–86.
3. Torbenson, M, et al. Glycogenic hepatopathy: an underrecognized hepatic complication of diabetes mellitus. *Am J Surg Pathol*. 2006; 30(4):508–513.

Fatty Liver of Pregnancy

KEY FACTS

Terminology

- Acute liver failure during 2nd half of pregnancy associated with severe fatty infiltration of liver

Etiology/Pathogenesis

- Etiology unknown but associated with mitochondrial fatty acid oxidation defects
  - Some affected mothers and infants have inherited long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency
  - Carnitine palmitoyltransferase I deficiency also associated with fatty liver of pregnancy

Clinical Issues

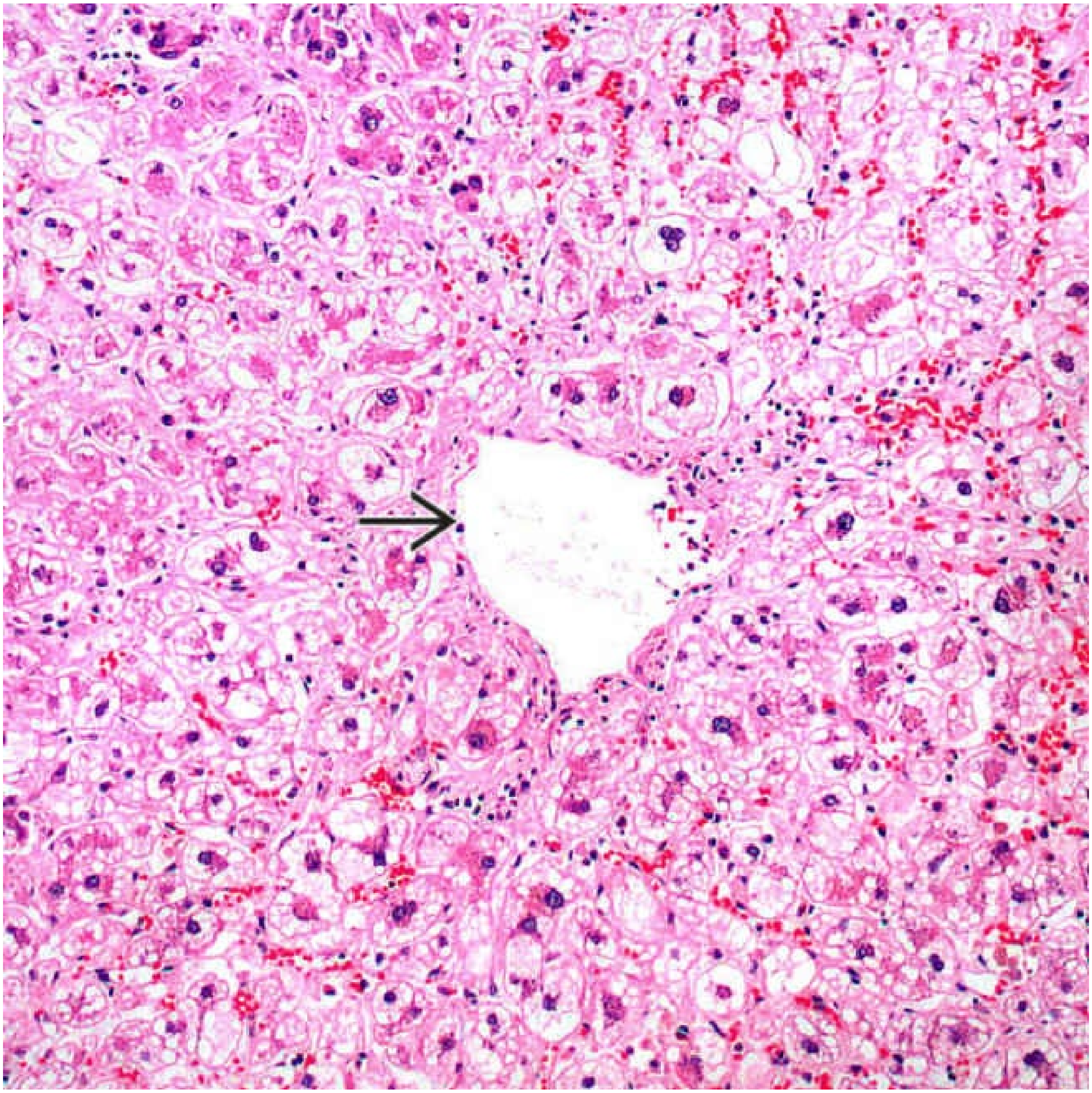
- Most commonly occurs in last 10 weeks and usually in last 4 weeks of pregnancy
  - Rapidly progressive acute liver failure
  - Early diagnosis and delivery are critical
  - Can be fatal for mother and fetus if not diagnosed and treated early
- Treatment
  - Supportive care and urgent delivery of infant
- Early diagnosis and delivery associated with excellent outcome

Microscopic

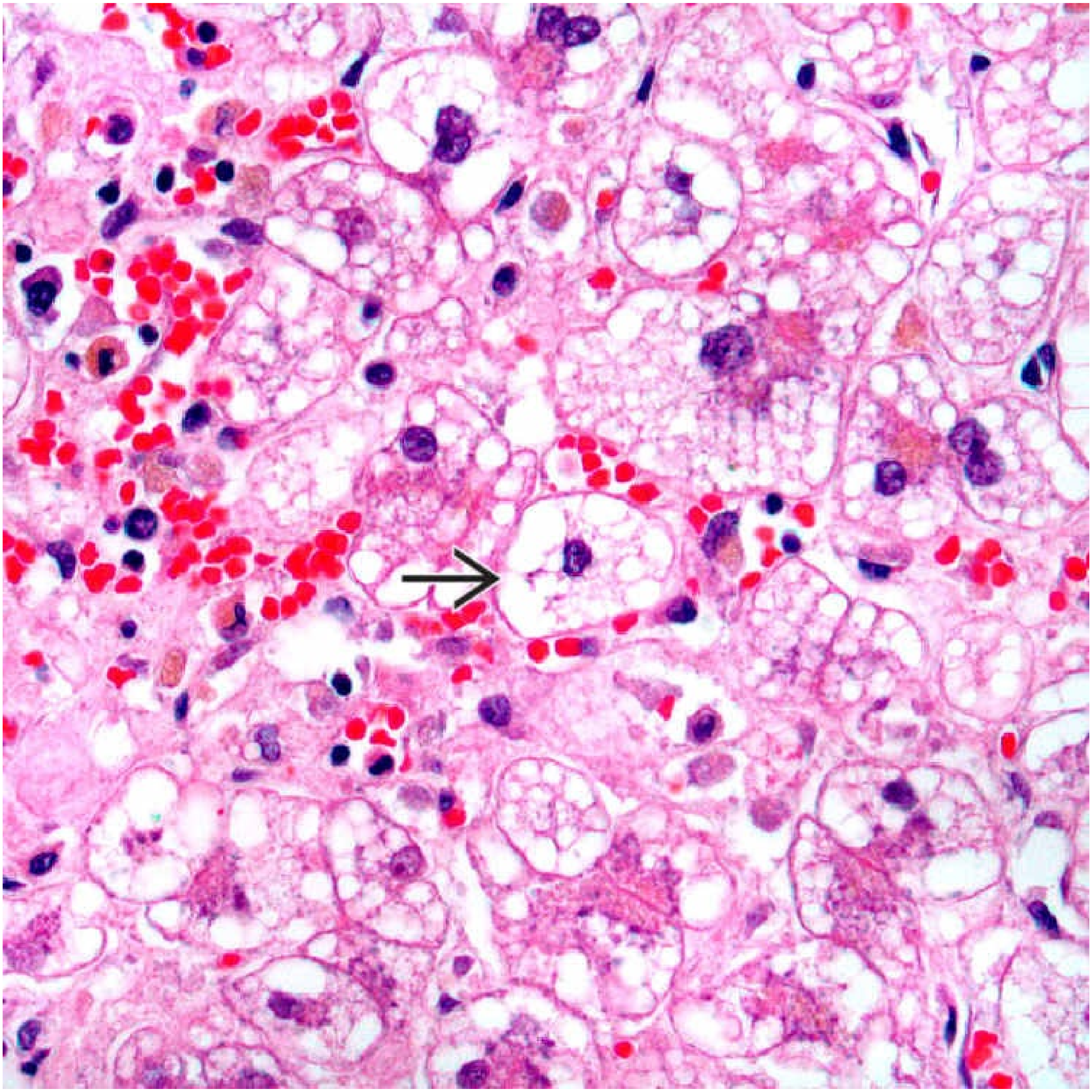
- Severe microvesicular steatosis, predominantly centrilobular or diffuse
  - May show small rim of periportal sparing
- Zone 3 perivenular canalicular cholestasis and hepatocellular cholestasis

Top Differential Diagnoses

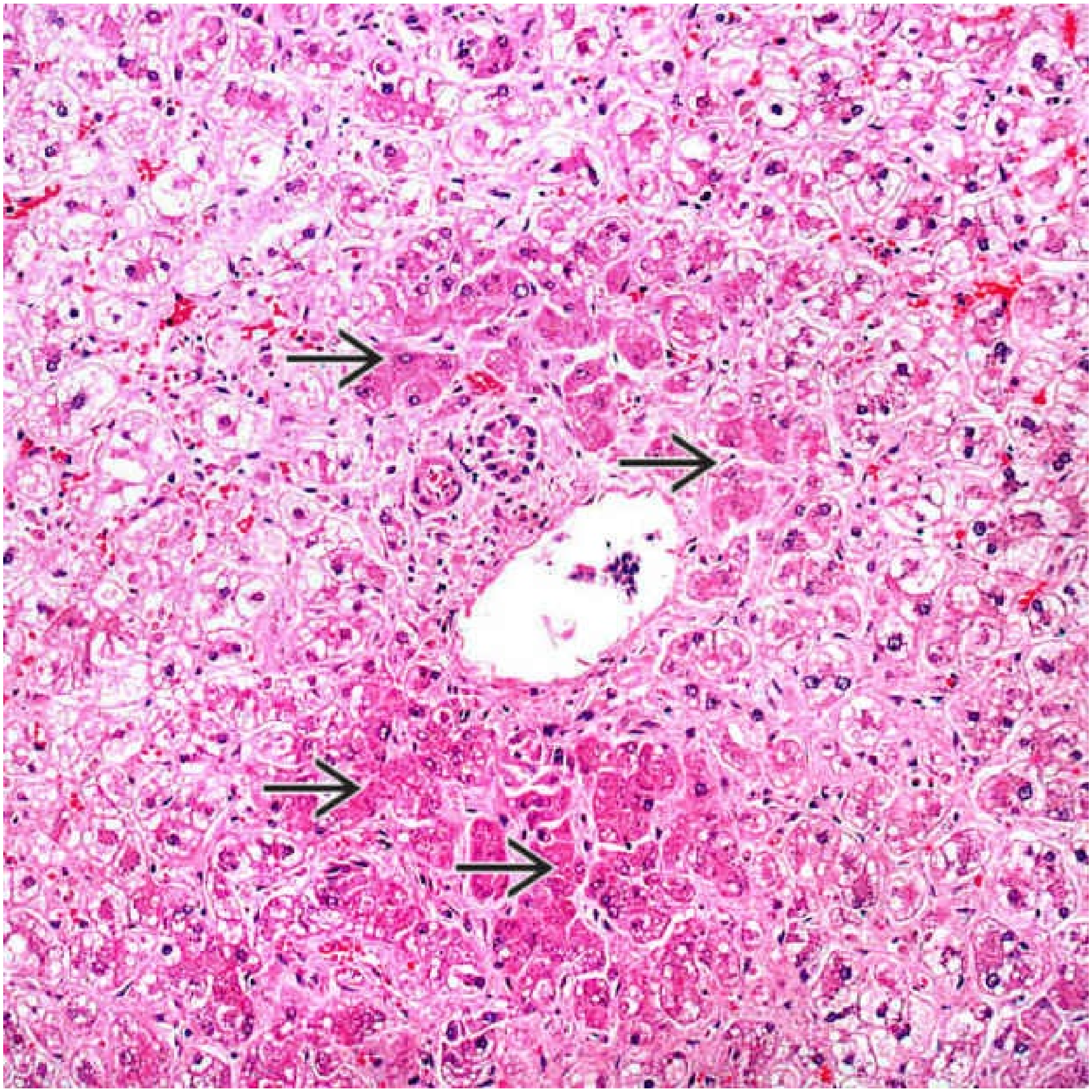
- Acute hepatic failure unrelated to pregnancy
- Preeclampsia/eclampsia



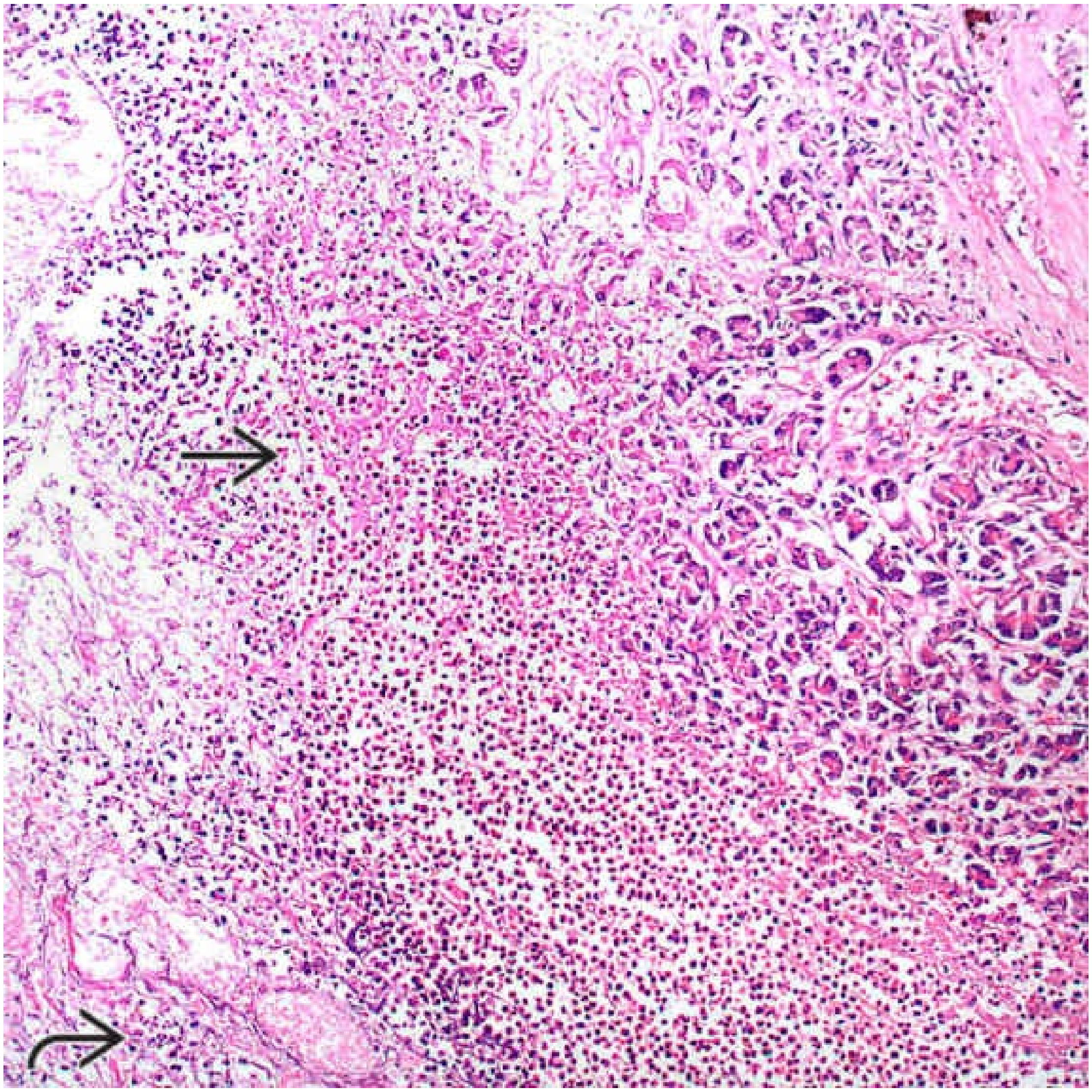
Centrilobular Microvesicular Steatosis
Extensive microvesicular steatosis involves the centrilobular or zone 3 hepatocytes. A central vein → is present in the center of the image.



Microvesicular Steatosis
High-power view demonstrates the extensive microvesicular steatosis typical of fatty liver of pregnancy. Numerous small steatotic vacuoles → surround and focally indent the hepatocyte nucleus.



Periportal Hepatocyte Sparing
There is a background of extensive microvesicular steatosis, but there is relative sparing of a small rim of periportal hepatocytes →.



Acute Pancreatitis in Fatty Liver of Pregnancy
Acute pancreatitis → with necrosis ↱ may also occur in patients with fatty liver of pregnancy.

TERMINOLOGY

Synonyms

- Acute fatty liver of pregnancy (AFLP)
- Hepatic lipidosis of pregnancy
- Sheehan syndrome

Definitions

- Acute liver failure during 2nd half of pregnancy with severe fatty infiltration of liver

ETIOLOGY/PATHOGENESIS

Etiology Unknown

- Attributed to mitochondrial fatty acid oxidation defect

- Some affected mothers and infants have inherited fatty acid oxidation defects
  - Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency
  - Infant and parents should be evaluated for LCHAD deficiency
- Carnitine palmitoyltransferase I deficiency also associated with fatty liver of pregnancy

CLINICAL ISSUES

Epidemiology

- Incidence
  - Diagnosed in 1/6,659 deliveries, although subclinical cases also exist
  - Usually occurs in late 3rd trimester but can be seen in 2nd trimester
  - More common in women who are primigravidae and have multiple gestations

Presentation

- Mild prodromal illness
- Nausea, vomiting, and abdominal pain
- Jaundice, cholestatic
- Confusion
- Rapidly progressive acute liver failure
- May also have hypertension and proteinuria
- Associated acute pancreatitis may also occur

Laboratory Tests

- Increased prothrombin time
- Low serum fibrinogen level
- Moderate hyperbilirubinemia and transaminase elevation
- Hypoglycemia
- Serum lipase and amylase elevated if acute pancreatitis also present

Natural History

- Does not progress to chronic liver disease
- Subsequent pregnancies may be unaffected or complicated by recurrent disease

Treatment

- Urgent delivery of infant
- Supportive therapy
- Transplantation in selected cases

Prognosis

- Can be fatal for mother and fetus if not diagnosed and treated early
  - Early diagnosis and delivery associated with excellent outcome
    - Up to 100% maternal survival rate
    - Infant mortality 6-7% or less

IMAGING

Radiographic Findings

- Ultrasound and CT demonstrate fatty infiltration of liver

MACROSCOPIC

General Features

- Liver grossly small and pale yellow

MICROSCOPIC

Histologic Features

- Severe microvesicular steatosis, predominantly centrilobular or diffuse
  - May show small rim of periportal hepatocyte sparing
  - Small steatosis vacuoles may require special stains (oil red O or Sudan black) to demonstrate, or electron microscopy
- Zone 3 perivenular canalicular cholestasis and hepatocellular cholestasis
- Hepatocyte injury and Kupffer cell hyperplasia
- Mild mononuclear infiltrates of lobules and portal tracts

DIFFERENTIAL DIAGNOSIS

Acute Hepatic Failure Unrelated to Pregnancy

- Acute viral hepatitis
- Drug-induced liver injury

Preeclampsia/Eclampsia

- Commonly also present in patients with AFLP
  - Hypertension and proteinuria
  - Periportal necrosis
    - In HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, also periportal hemorrhage and fibrin deposition
- Both disorders treated by delivery

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Microvesicular steatosis in pregnant woman with acute liver failure

SELECTED REFERENCES

1. Goel, A, et al. Pregnancy-related liver disorders. *J Clin Exp Hepatol*. 2014; 4(2):151–162.
2. Gutiérrez Junquera, C, et al. Acute fatty liver of pregnancy and neonatal long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) deficiency. *Eur J Pediatr*. 2009; 168(1):103–106.
3. Devarbhavi, H, et al. Pregnancy-associated acute liver disease and acute viral hepatitis: differentiation, course and outcome. *J Hepatol*. 2008; 49(6):930–935.
4. Hay, JE. Liver disease in pregnancy. *Hepatology*. 2008; 47(3):1067–1076.
5. Knight, M, et al. A prospective national study of acute fatty liver of pregnancy in the UK. *Gut*. 2008; 57(7):951–956.

SECTION 7
VASCULAR DISORDERS

OUTLINE

Portal Venous Obstruction

KEY FACTS

Etiology/Pathogenesis

- Can occur at any level of portal venous system
  - Extrahepatic
  - Portal vein thrombosis
  - Reduced portal flow velocity (stasis)
  - Vascular injury
  - Tumor thrombosis
  - Extrinsic compression by mass or fibrogenic lesions
  - Congenital vascular anomalies
- Intrahepatic
  - Propagation of large portal vein thrombosis or emboli
  - Diseases that affect small portal veins
  - Specific etiology may not be identifiable

Clinical Issues

- 5-10% in patients with portal hypertension in developed countries
- Sequelae depend on location, cause, time course, and extent of blockage

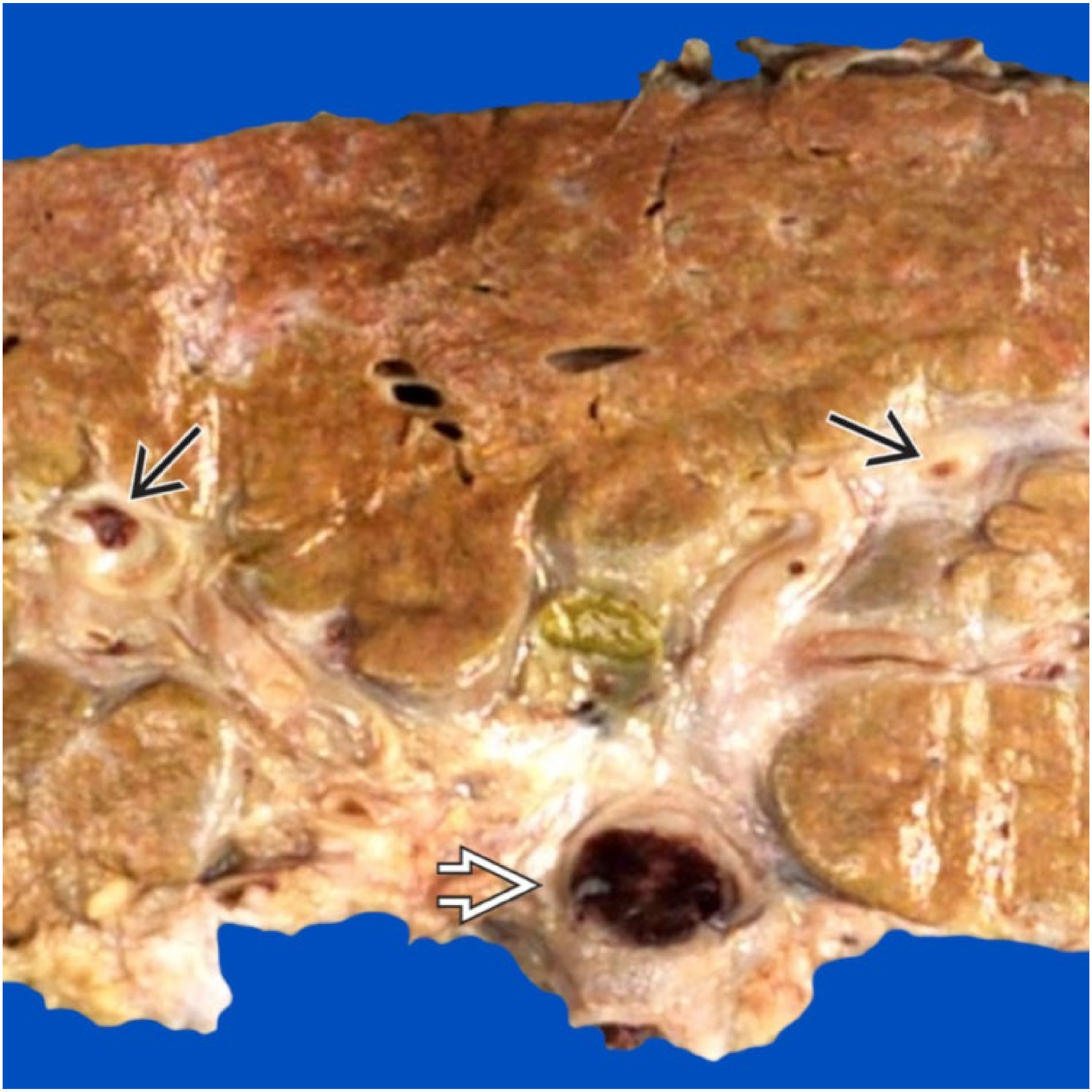
Microscopic

- Often inconsistent or irregularly distributed, may be missed in biopsy specimens
  - Subtle alterations of portal venules
  - Dilated portal venules
  - Multiple collateral venules
  - Herniation of portal venules into parenchyma
  - Obliteration of portal venules, similar to hepatoportal sclerosis, may be seen
- Infarcts of Zahn
  - Persistent occlusion can lead to atrophy of entire segments of liver
  - True infarcts rarely develop
- Nodular regenerative hyperplasia may be seen

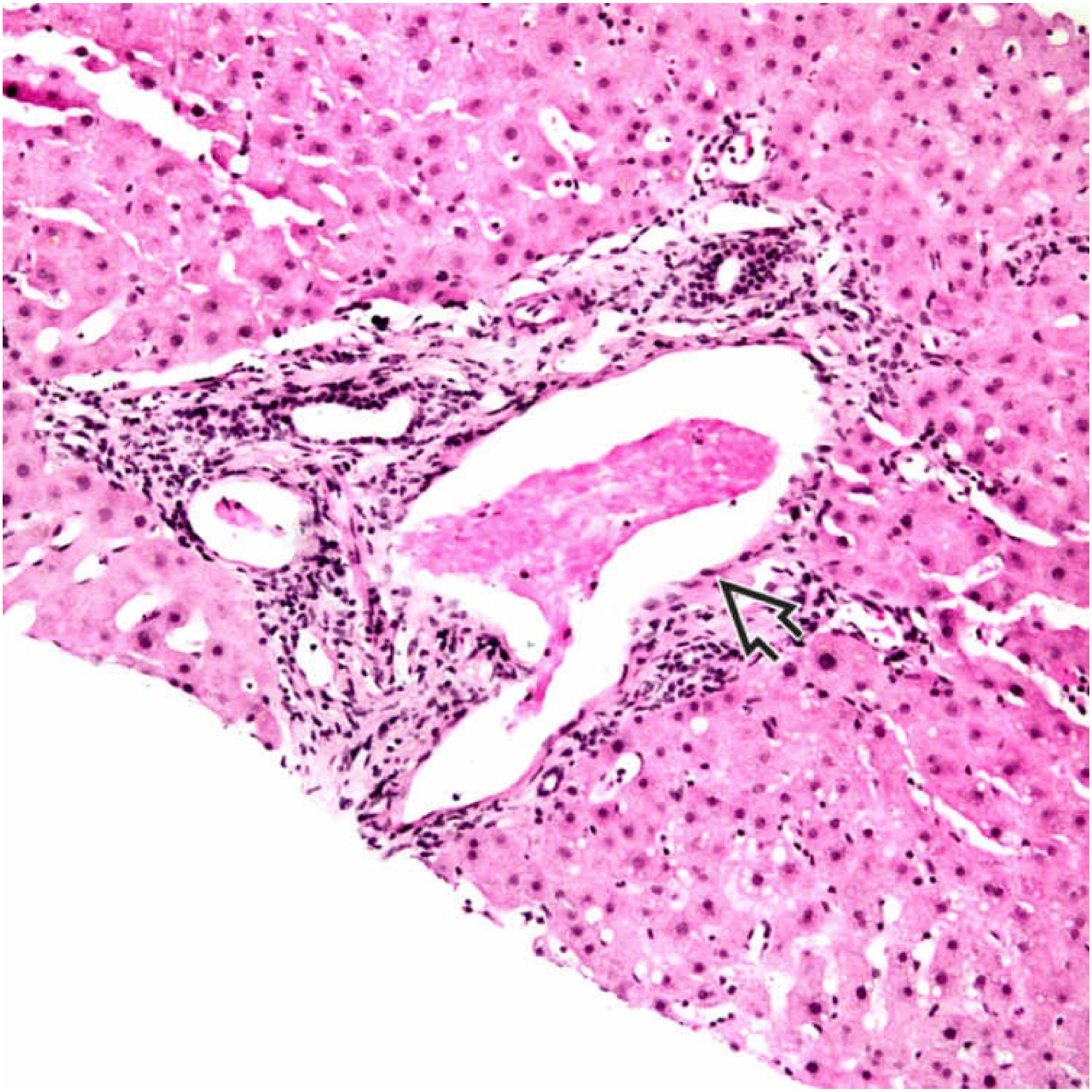
• Findings suggestive of underlying etiologies

Top Differential Diagnoses

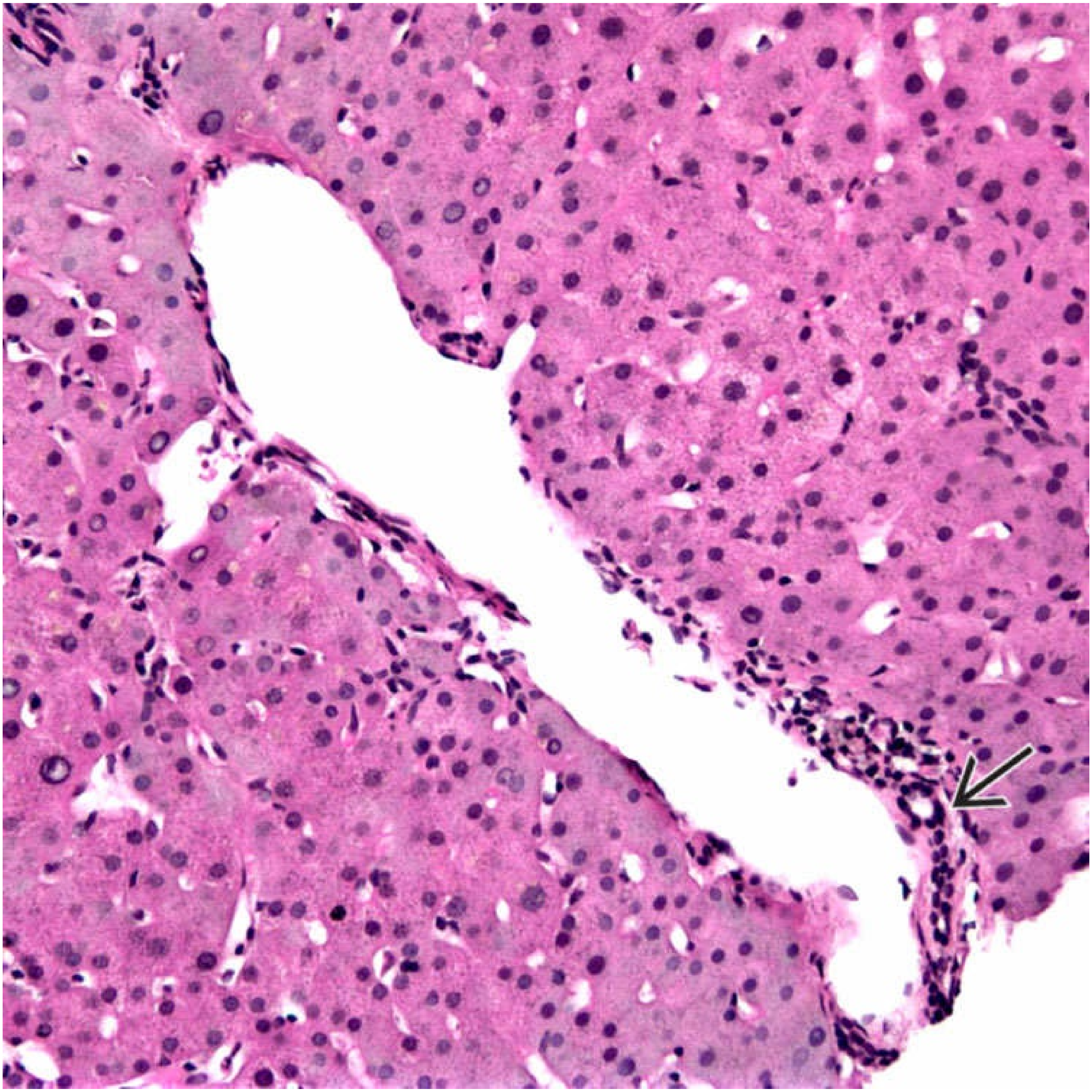
• Hepatoportal sclerosis
• Normal liver



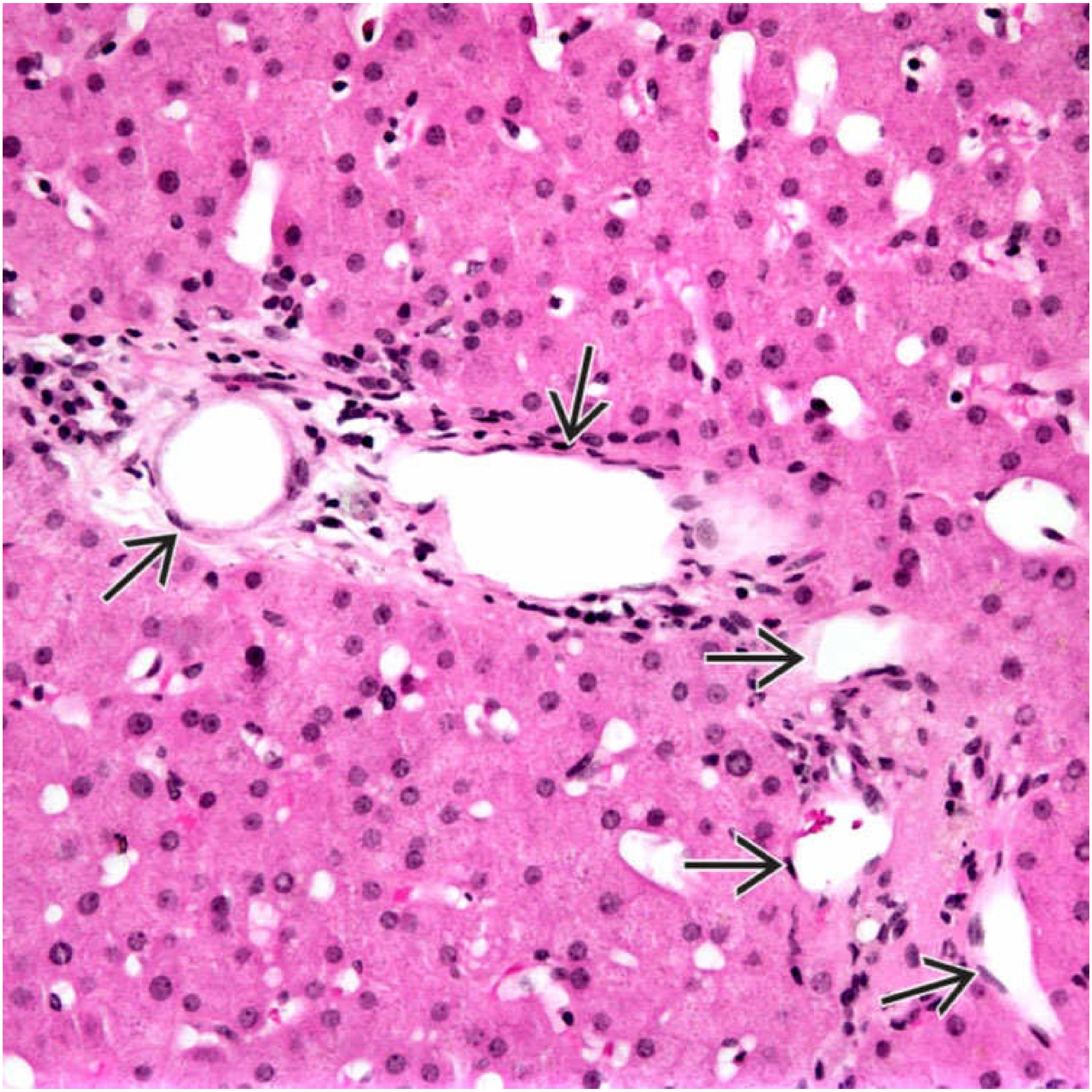
Portal Vein Thrombosis
Gross photograph of this liver explant shows a large portal vein thrombus ⇨ in the hilar region. Propagation into smaller intrahepatic portal veins → is also grossly noticed.



Dilated Portal Venule
This microphotograph shows a markedly dilated portal venule ⇨ in the setting of portal vein thrombosis.
Note the presence of fibrin thrombus in the lumen.



Herniated Portal Venule
Typical changes in portal venous obstruction include dilated portal venules with “herniation” of the vessel into the surrounding parenchyma. Note the presence of a bile duct → in compressed portal stroma.



Collateral Venules
Multiple collateral venules → are present in this portal tract in a case of portal venous obstruction indicating elevated portal pressures.

TERMINOLOGY

Synonyms

- Idiopathic portal hypertension
  - Many cases of idiopathic portal hypertension probably represent undetected portal vein thrombosis
- Noncirrhotic portal hypertension

Definitions

- Mechanical obstruction of portal venous system
  - Extrahepatic
  - ○ Obstruction of portal vein trunk or its main tributaries
- Intrahepatic
  - ○ Obstruction of portal venules within liver

ETIOLOGY/PATHOGENESIS

Extrahepatic

- Portal vein thrombosis
  - ○ Hypercoagulable states
  - – Inherited
  - □ Protein C or S deficiency, antithrombin III deficiency, factor V Leiden, etc.

– Acquired

□ Chronic myeloproliferative diseases, oral contraceptive use, pregnancy, antiphospholipid syndrome, etc.

○ Reduced portal flow velocity (stasis)

– Cirrhosis, venous outflow obstruction, etc.

○ Vascular injury

– Intraabdominal procedures or inflammation

- Tumor thrombosis
- Extrinsic compression by mass or fibrogenic lesions
- Congenital vascular anomalies

Intrahepatic

- Propagation of large portal vein thrombosis or emboli
  - Diseases that affect small portal veins
  - ○ Sarcoidosis, schistosomiasis, congenital hepatic fibrosis, primary biliary cholangitis, vasculotoxic chemicals, any types of cirrhosis
- Specific etiology may not be identifiable

CLINICAL ISSUES

Epidemiology

- Incidence
  - ○ Portal vein thrombosis occurs in 1% of population
  - – 5-10% in patients with portal hypertension in developed countries
- Age

- Both children and adults can be affected

Presentation

- Signs/symptoms of portal hypertension
  - Abdominal pain/tenderness/distension, splenomegaly, varices, ascites
- Complications
  - Variceal bleeding, liver failure, ischemic bowel
  - Portal biliopathy
    - Partial biliary obstruction similar to sclerosing cholangitis due to either compression by collateral veins, distortion by fibrous scarring or ischemic injury
- May be asymptomatic
  - May be well tolerated because of liver dual blood supply and development of collaterals
- Sequelae depend on location, cause, time course, and extent of blockage

Treatment

- Managing sequelae of portal hypertension
- Treating underlying cause of obstruction if possible
- Thrombectomy

Prognosis

- Determined by underlying cause as well as location, time course, extent of obstruction

IMAGING

Radiographic Findings

- Absence of blood flow in portal vein by Doppler ultrasound
- Direct visualization of obstruction by CT, MR, or angiography
- Intrahepatic obstruction may not be apparent on noninvasive imaging studies

MACROSCOPIC

Large Vessel Findings

- Fresh, organizing or organized thrombi ± mural calcifications
- Cavernous transformation or portal cavernoma (mass of collateral and recanalized vessels)

MICROSCOPIC

Histologic Features

- Often inconsistent or irregularly distributed, may be missed in biopsy specimens

- Subtle alterations of portal venules
  - Dilated portal venules
  - Multiple collateral venules
  - Herniation of portal venules into parenchyma
  - Obliteration of portal venules, similar to hepatoportal sclerosis, may be seen
- Infarcts of Zahn
  - Not really infarcts but rather zones of hepatocyte atrophy with sinusoidal dilatation and congestion
  - Persistent occlusion can lead to atrophy of entire segments of liver
  - True infarcts rarely develop
- Nodular regenerative hyperplasia may be seen
- Findings suggestive of underlying etiologies
  - Granulomas, *Schistosoma* eggs, etc.

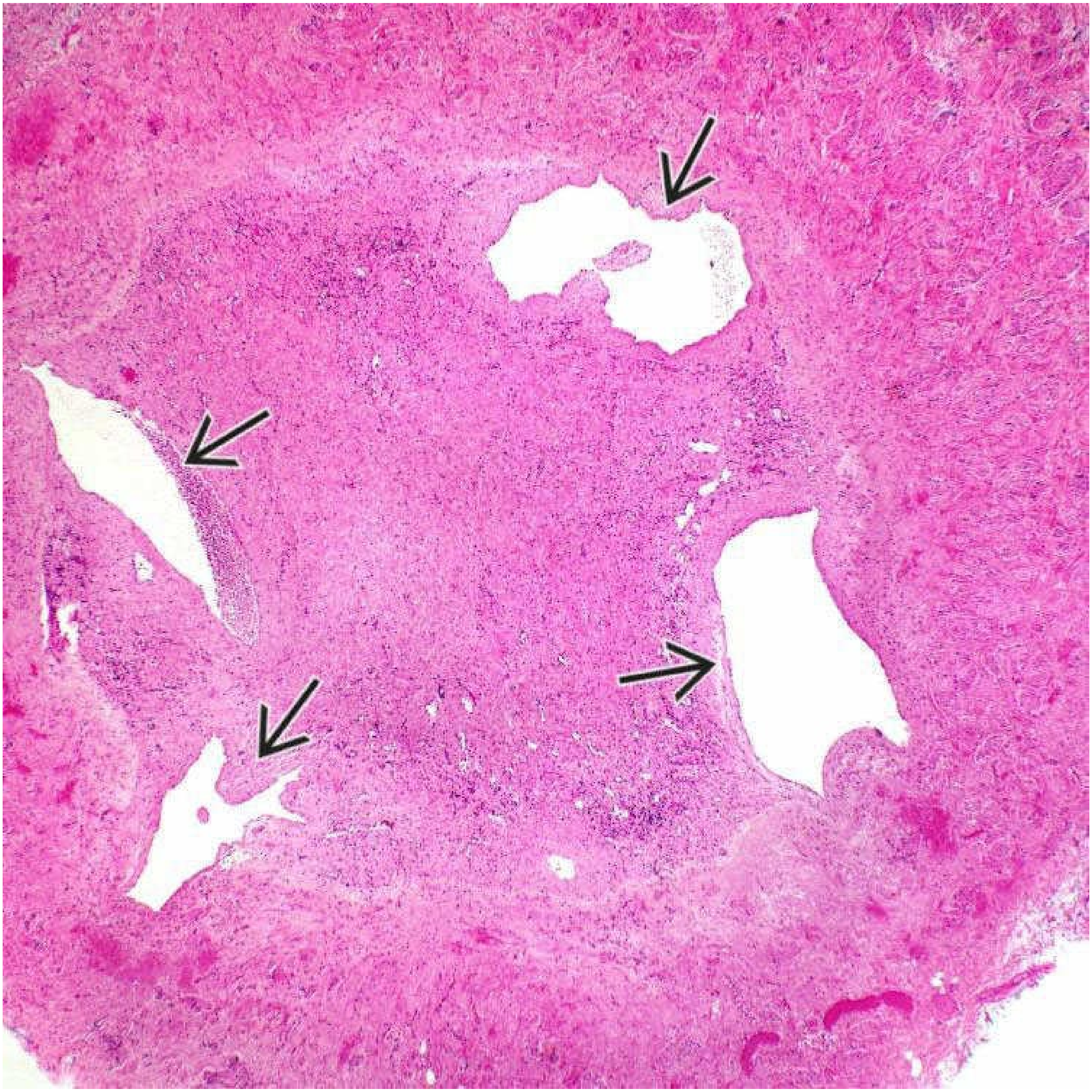
DIFFERENTIAL DIAGNOSIS

Hepatoportal Sclerosis

- Abnormal hepatic architecture
- May show homozygous mutations in *DGUOK* gene

Normal Liver

- Obliteration of small number of intrahepatic portal venules is normal finding in elderly persons



This extrahepatic portal vein is completely obliterated by organized thrombus, but several irregular channels are present →, indicating recanalization.

SELECTED REFERENCES

1. Vilarinho, S, et al. Recurrent recessive mutation in deoxyguanosine kinase causes idiopathic noncirrhotic portal hypertension. *Hepatology*. 2016; 63(6):1977–1986.
2. Kumar, A, et al. Review article: portal vein obstruction–epidemiology, pathogenesis, natural history, prognosis and treatment. *Aliment Pharmacol Ther*. 2015; 41(3):276–292.

Hepatoportal Sclerosis

KEY FACTS

Terminology

- Portal hypertension secondary to portal fibrosis and portal vein obliteration
  - Form of noncirrhotic portal hypertension

Etiology/Pathogenesis

- Associated with conditions that cause increased vascular resistance at presinusoidal level
  - Genetic predisposition
  - Chronic exposure to toxins and medications
  - Prothrombotic states
  - Autoimmune disorders
  - Many cases idiopathic

Clinical Issues

- Up to 40% of patients with portal hypertension in India and Japan
  - Increasingly recognized in Western countries
- Most common in young and middle-aged adults
- Better prognosis than cirrhotic portal hypertension because of preserved liver function
- Typically presents with signs of portal hypertension
  - Usually normal or near normal liver function tests

Macroscopic

- Normal, enlarged, or shrunken liver with irregular, wrinkled capsular surface
- Dilatation and mural thickening of large portal veins

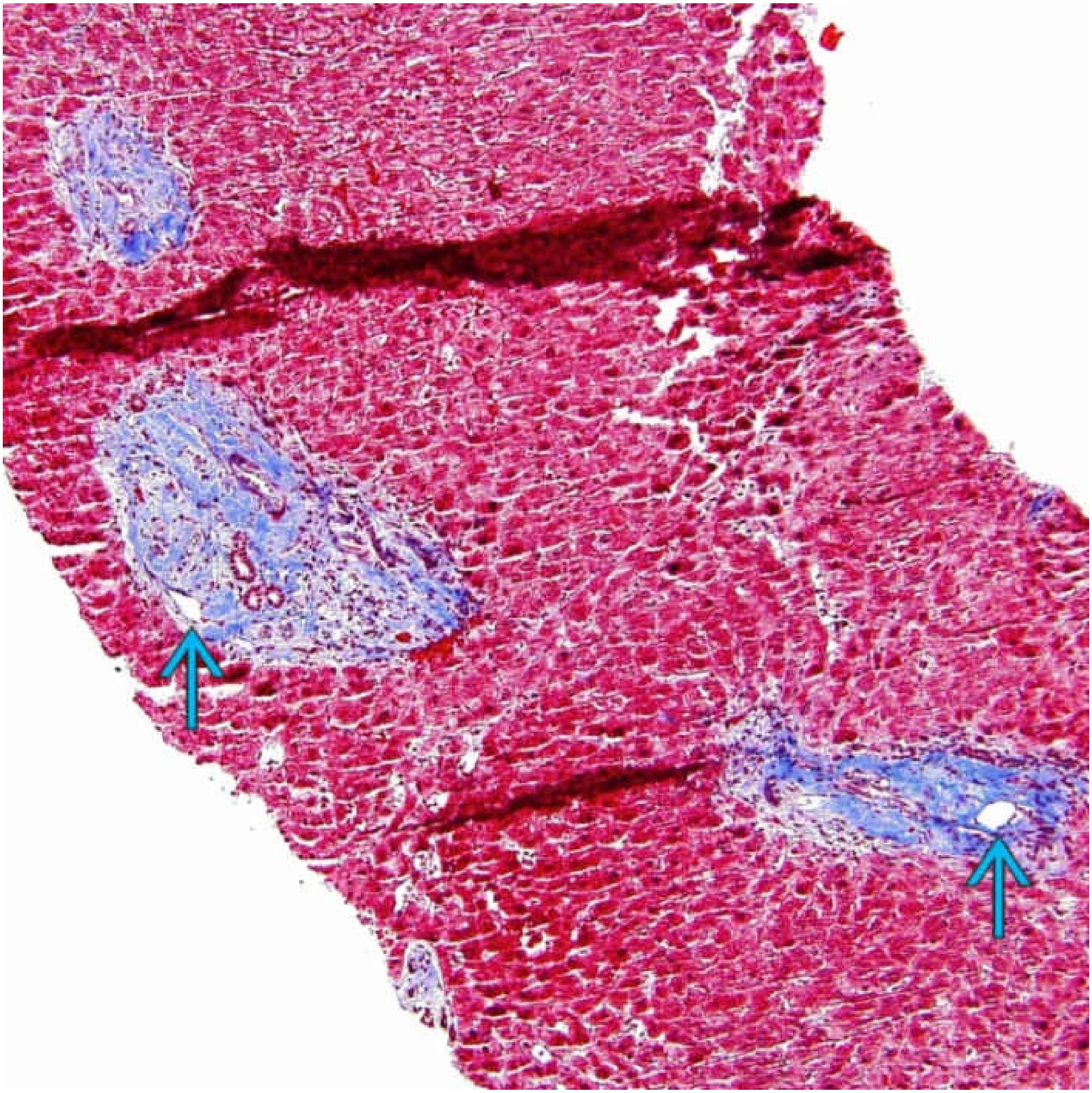
Microscopic

- Abnormal hepatic architecture with lack of consistent relationship between portal tracts and central

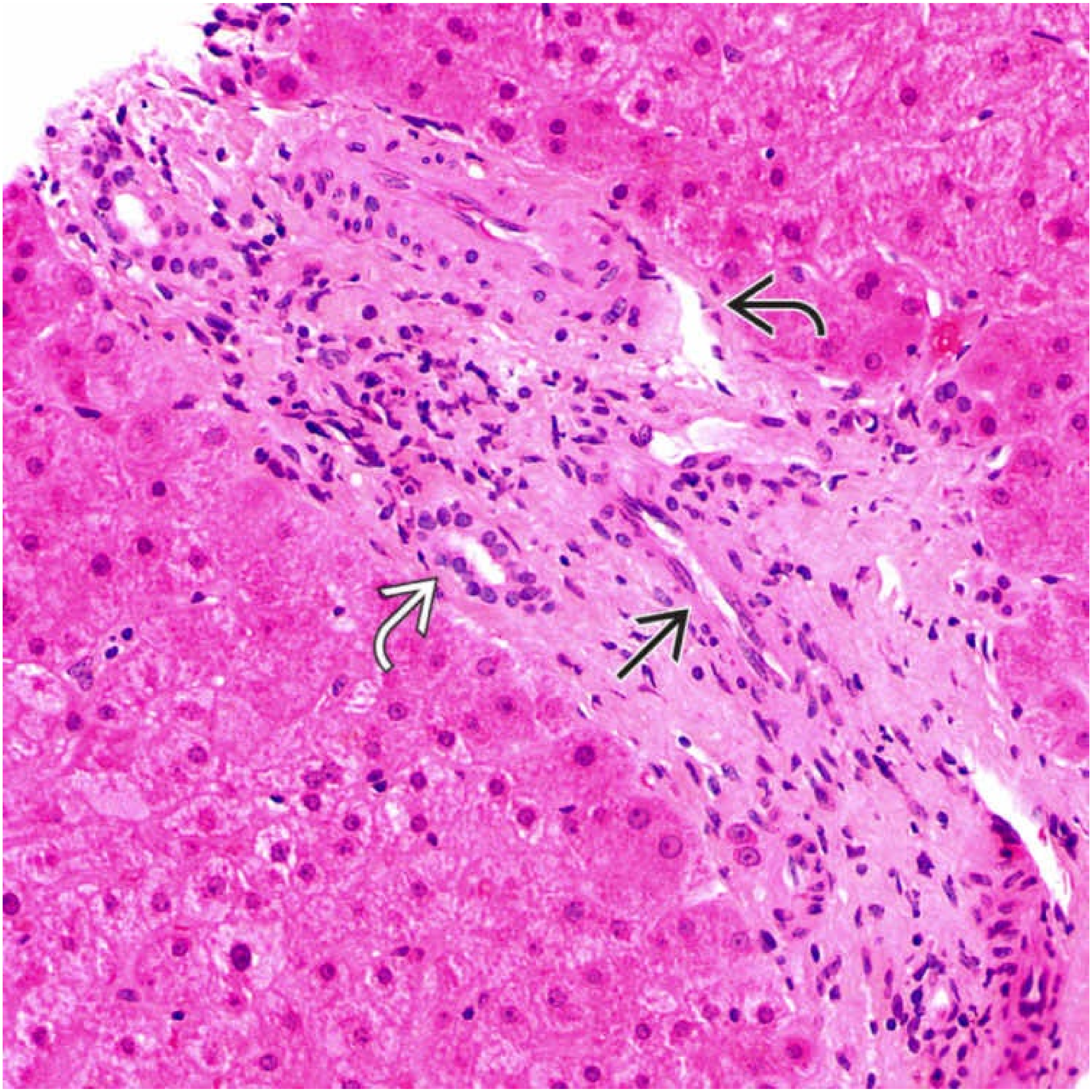
veins

• Portal fibrosis
• Narrowing or obliteration of portal veins (phlebosclerosis)
• Concomitant nodular regenerative hyperplasia may be present

Macroscopic Features by MR Imaging
Abdominal MR shows an irregular hepatic surface with a shrunken appearance ⇨ and heterogeneous hepatic parenchyma due to portal fibrosis. Note the presence of splenomegaly ↪ .

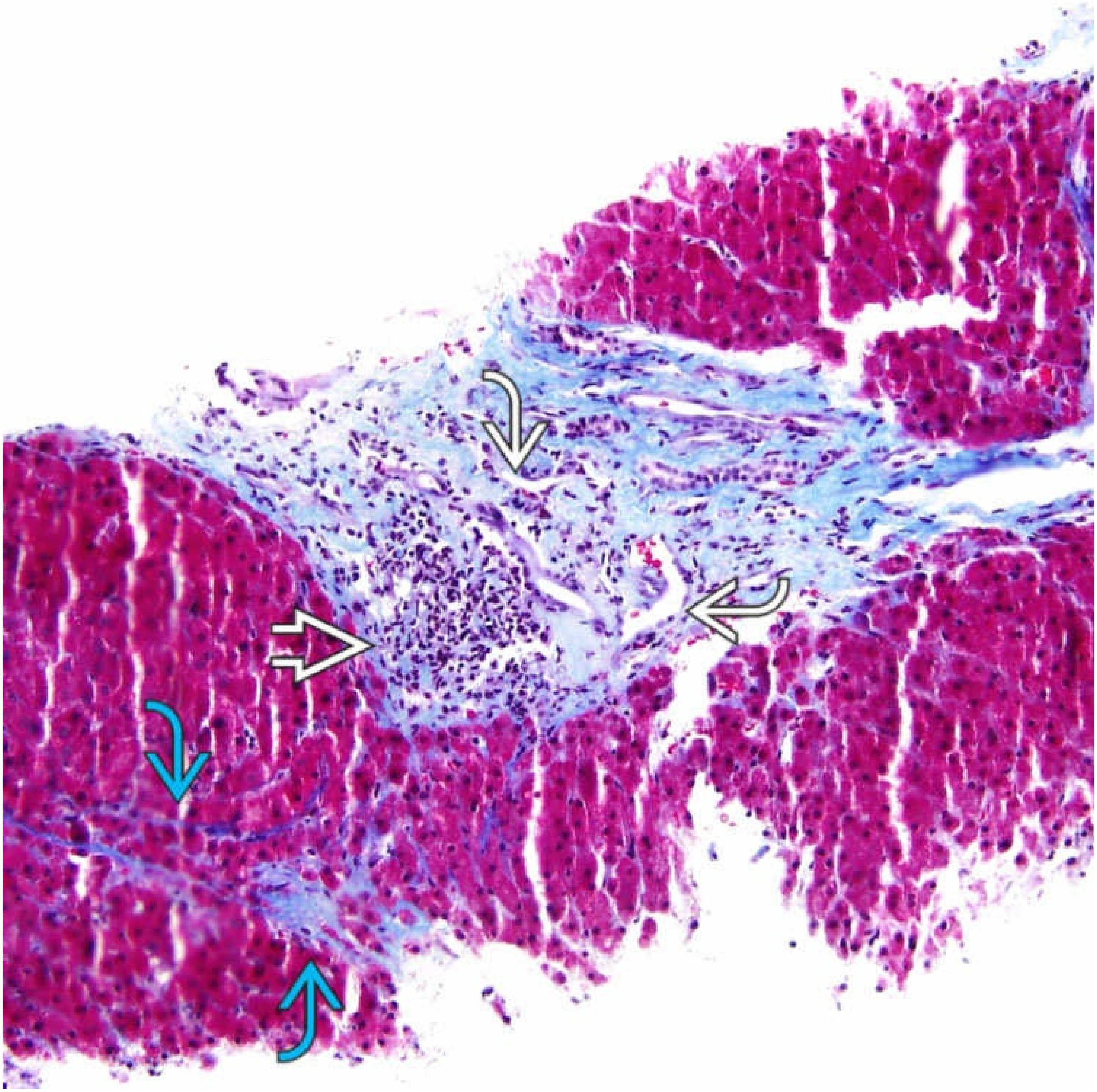


Abnormal Hepatic Architecture
Trichrome stain highlights abnormal approximation of portal tracts seen in a needle biopsy from a patient with portal hypertension. Portal fibrosis and narrowed portal veins → are evident. No central veins are seen between portal tracts in this field. Note the absence of cirrhosis.



Portal Fibrosis

This portal tract is expanded by fibrosis, with marked narrowing of the portal vein. Note the presence of normal-caliber hepatic artery and bile duct. There are no significant inflammatory cell infiltrates in the portal tract.



Portal and Perisinusoidal Fibrosis
This portal tract shows marked fibrosis, minimal inflammatory cell infiltrates, and multiple slit-like spaces representing narrowed portal veins. Focal perisinusoidal collagen deposition is also noted in this biopsy.

TERMINOLOGY

Abbreviations

• Hepatoportal sclerosis (HPS)

Synonyms

- Obliterative portal venopathy
- Intrahepatic portal venopathy
- Idiopathic presinusoidal portal hypertension
- Banti disease or Banti syndrome

Definitions

- Portal hypertension secondary to portal fibrosis and portal vein obliteration in absence of cirrhosis
  - Form of noncirrhotic portal hypertension

ETIOLOGY/PATHOGENESIS

Multifactorial

- Associated with conditions that cause increased vascular resistance at presinusoidal level
  - Genetic predisposition (Adams-Oliver syndrome)
  - Chronic exposure to toxins or medications (e.g., inorganic arsenic, vinyl chloride, mercaptopurine, didanosine)
  - Intestinal and intraabdominal bacterial infections
  - Prothrombotic states
  - Autoimmune disorders
  - Many cases idiopathic

CLINICAL ISSUES

Epidemiology

- Incidence
  - Up to 40% of patients with portal hypertension in India and Japan
  - 3-5% in Western countries, but increasingly recognized in recent years
- Age
  - Most common in young and middle-aged adults (25-56 years), but can occur in children

Presentation

- Variceal bleeding, splenomegaly
  - Due to elevated portal venous pressure
- Jaundice, ascites and encephalopathy in advanced disease

Laboratory Tests

- Usually normal or near normal liver function tests
- Anemia and thrombocytopenia

Treatment

- Transjugular intrahepatic portosystemic shunt (TIPS)
- Splenectomy
- Anticoagulant
- Liver transplantation for advanced disease

Prognosis

- Better than cirrhosis because of preserved liver function

IMAGING

General Features

- Sudden narrowing or paucity of intrahepatic portal vein branches (withered-tree appearance)
- Patent extrahepatic portal and hepatic veins
- Portal vein thrombosis may be seen

MACROSCOPIC

General Features

- Normal, enlarged, or shrunken liver
- Irregular, nodular, or wrinkled capsular surface
- Dilatation and mural thickening of large portal veins
- Old thrombi may be seen in portal vein branches

MICROSCOPIC

Histologic Features

- Abnormal hepatic architecture
    - Distorted portal-central vein relationships (approximation or wide separation)
    - Eccentric location of central veins in lobules, or multiple ectatic veins in single lobule
- Portal vein changes
    - Narrowing or obliteration of portal veins (phlebosclerosis)
    - Presence of numerous thin-walled vascular channels in portal tracts (angiomatoid malformation)
    - Herniation of normal caliber or dilated portal veins into lobule (paraportal shunt vessels)
- Portal fibrosis
    - Periportal and perisinusoidal fibrosis as well as slender portal-portal fibrous septa may be seen
- Marked sinusoidal dilatation (megasinusoids)
- Minimal portal inflammation
- Diffuse or localized nodular regenerative hyperplasia

DIFFERENTIAL DIAGNOSIS

Portal Venopathy Without Portal Hypertension

- Unclear clinical significance, but may represent early stage of disease in some cases
- Correlates with increased fibrosis in hepatitis C patients
- Frequently seen in allograft biopsies
- Absence of portal hypertension must be clinically documented

Portal Vein Thrombosis

- May have similar histologic features
- Demonstrate thrombus through imaging studies

Nodular Regenerative Hyperplasia

- Nodular liver due to alternating areas of hepatic plate hypertrophy and atrophy, but no fibrosis
  - Normal-appearing portal tracts and portal veins
  - May coexist with hepatoportal sclerosis

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Rule out other possible etiologies of portal hypertension, especially cirrhosis

SELECTED REFERENCES

1. Guido, M, et al. Obliterative portal venopathy without portal hypertension: an underestimated condition. *Liver Int*. 2016; 36(3):454–460.
2. Arora, A, et al. Multimodality imaging of obliterative portal venopathy: what every radiologist should know. *Br J Radiol*. 2015; 88(1046):20140653.
3. Franchi-Abella, S, et al. Obliterative portal venopathy: a study of 48 children. *J Pediatr*. 2014; 165(1):190–193.e2.
4. Aggarwal, S, et al. Obliterative portal venopathy: a clinical and histopathological review. *Dig Dis Sci*. 2013; 58(10):2767–2776.
5. Krasinskas, AM, et al. Abnormal intrahepatic portal vasculature in native and allograft liver biopsies: a comparative analysis. *Am J Surg Pathol*. 2005; 29(10):1382–1388.

Hepatic Venous Outflow Obstruction

KEY FACTS

Etiology/Pathogenesis

- Sinusoids or small hepatic veins: Sinusoidal obstruction syndrome (formerly venoocclusive disease)
- Large hepatic veins or inferior vena cava (Budd-Chiari syndrome)
- Right heart or pericardial disease

Clinical Issues

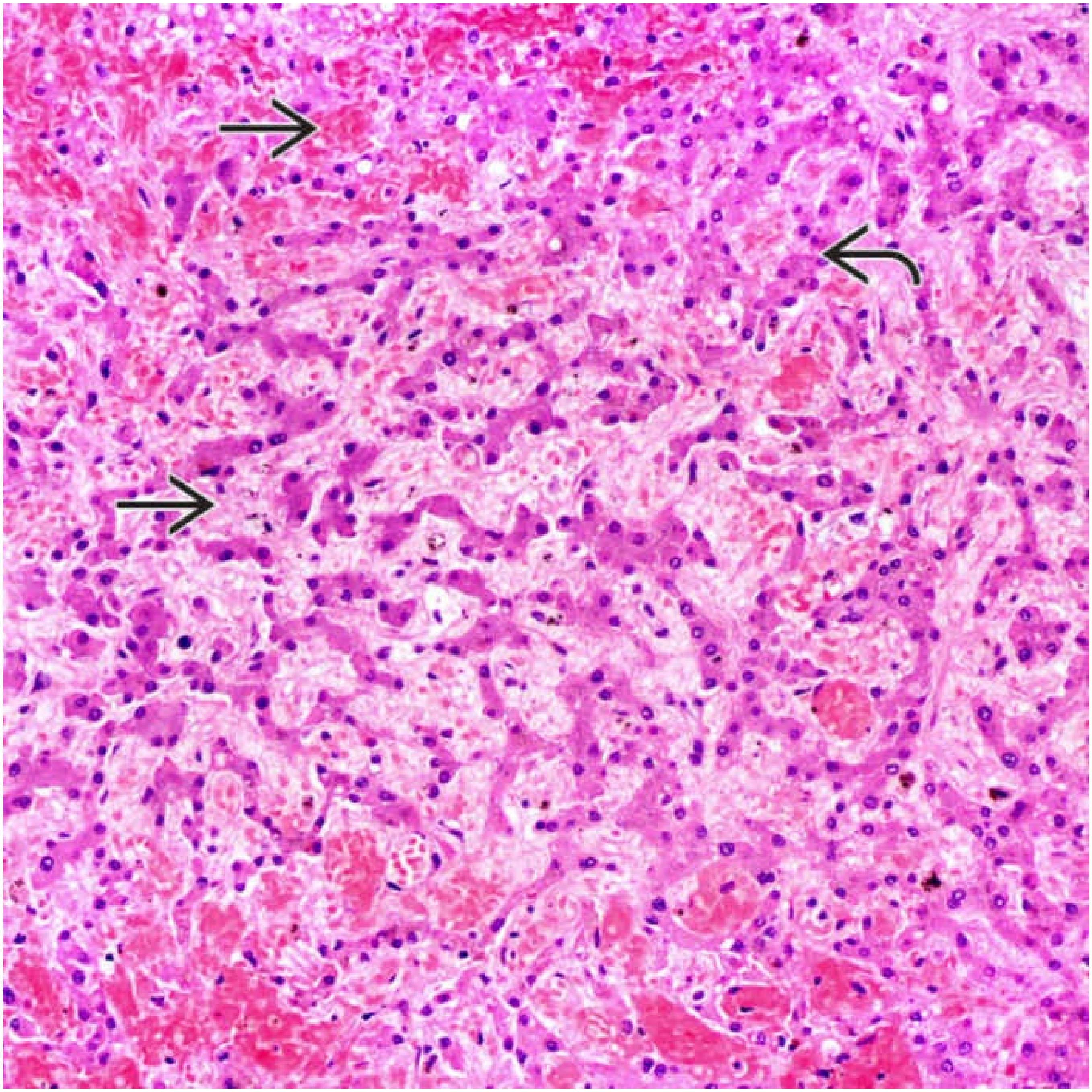
- Subacute presentation (< 6 months) is most common with painful hepatomegaly, mild jaundice, and ascites
- Less commonly, disease presents as chronic liver disease or cirrhosis
- Rare cases have fulminant presentation with acute liver failure

Microscopic

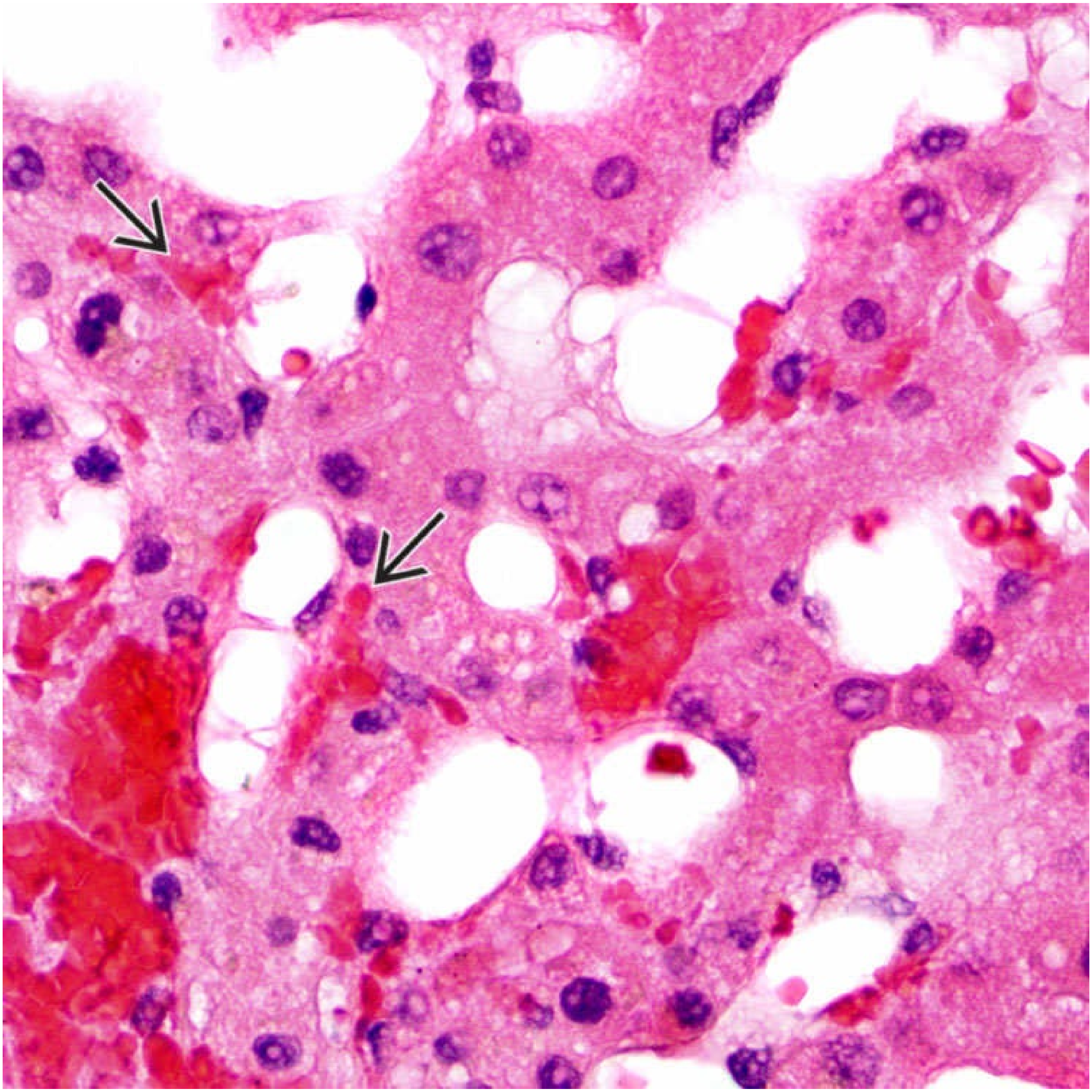
- Centrizonal-based changes: Sinusoidal dilatation and congestion, RBC extravasation, hepatic plate atrophy, necrosis
- Portal-based changes: Ductular reaction, focal bile duct damage
- Central vein-based fibrosis in chronic cases
- Nodular regenerative hyperplasia can occur
- Large regenerative nodules in BCS

Top Differential Diagnoses

- Biliary disease
  - Other diseases that can cause sinusoidal dilatation
    - Portal vein thrombosis, systemic inflammatory conditions, some neoplasms such as renal cell carcinoma or lymphoma, artifactual sinusoidal dilatation
- Other causes of parenchymal necrosis/hemorrhage
    - Acetaminophen toxicity, ischemic liver injury

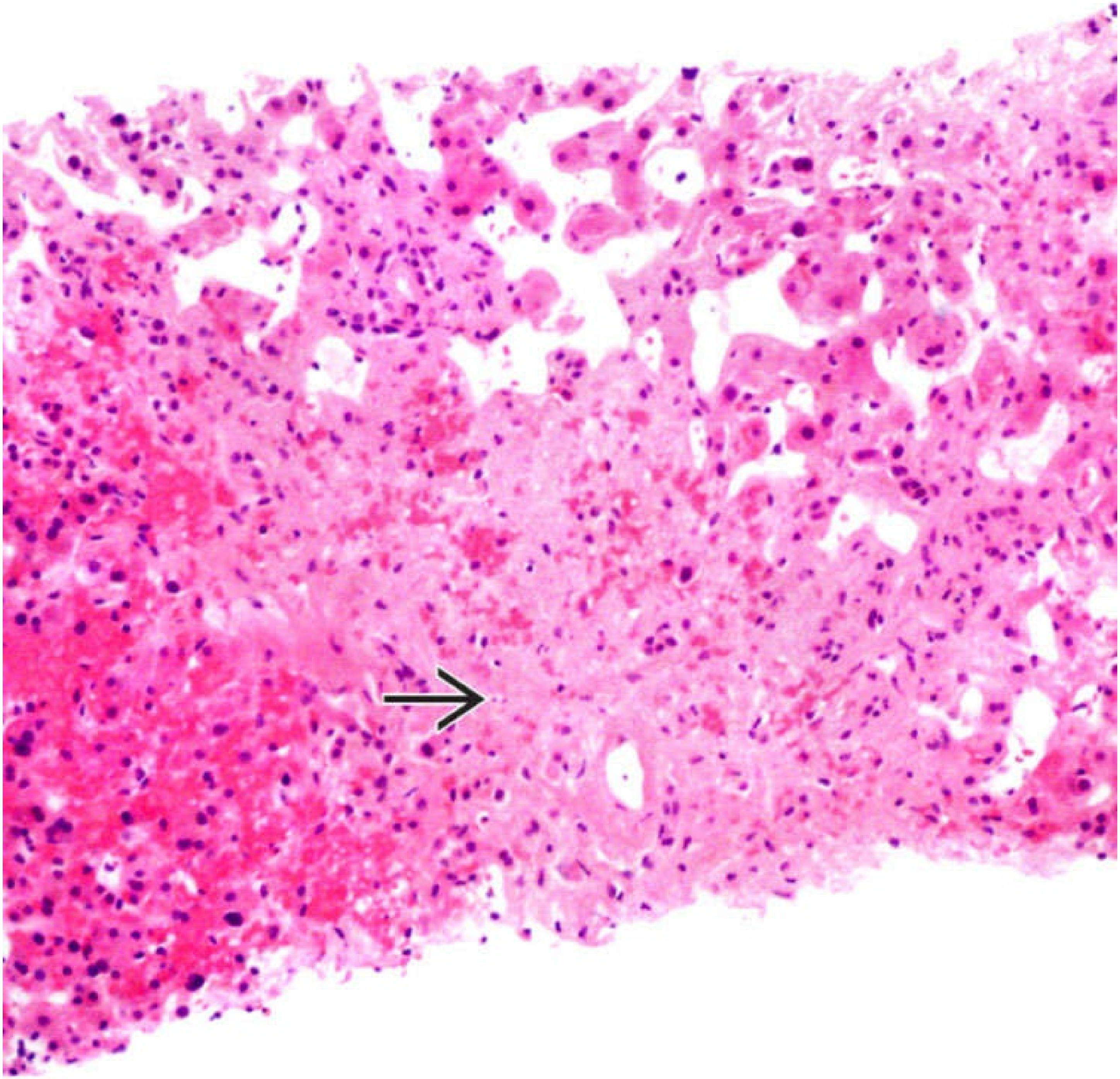


Sinusoidal Dilatation
In Budd-Chiari syndrome, increased sinusoidal pressure causes sinusoidal dilatation, congestion →, and hepatocellular atrophy ↱ .

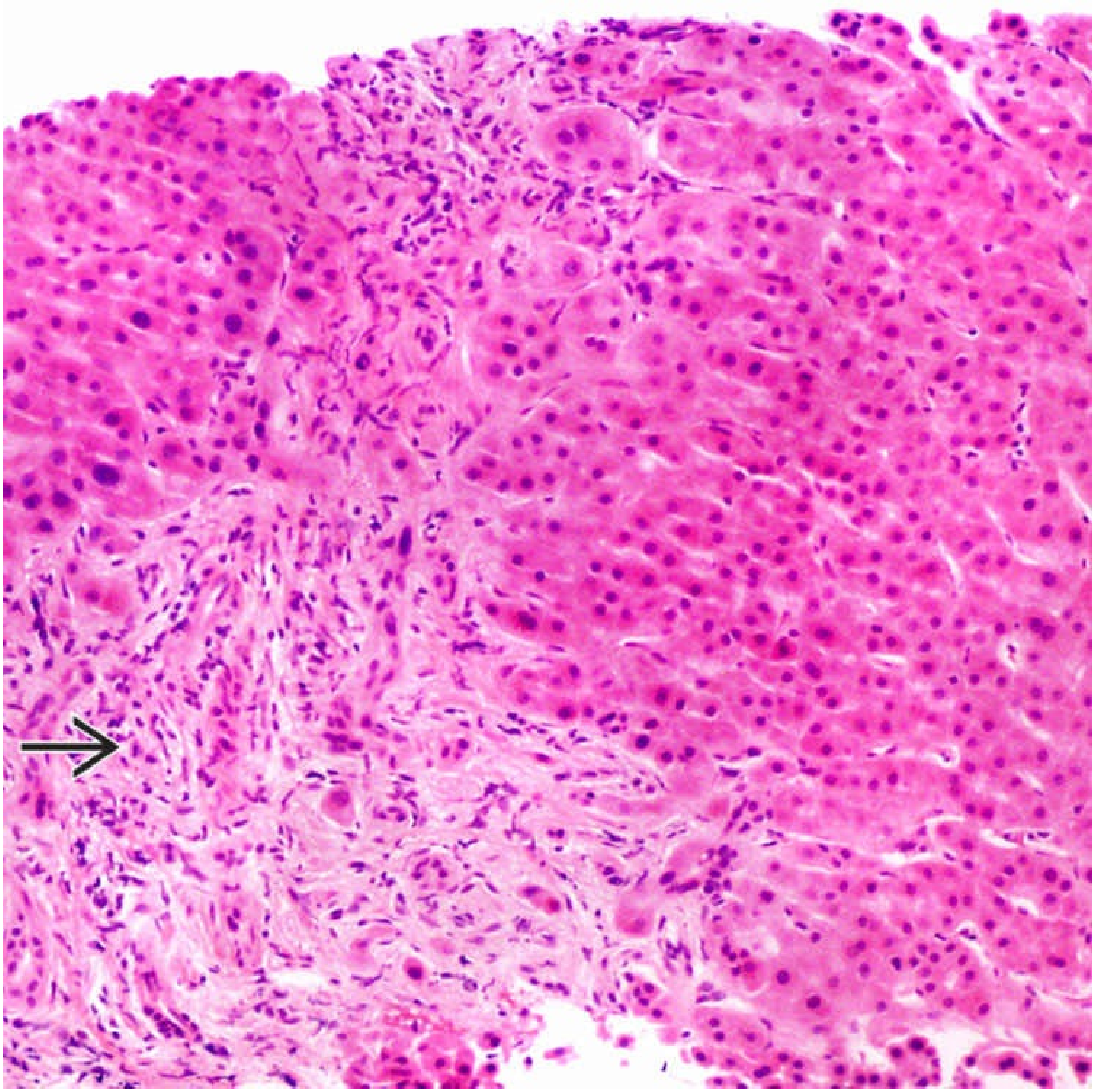


RBC in Space of Disse

Extravasation of RBC → in the space of Disse (the potential space between the hepatocytes and sinusoidal basement membrane) is caused by increased sinusoidal pressure.



Hemorrhagic Necrosis
Hepatocellular necrosis → around the central vein can be seen in HVOO, especially in cases presenting acutely. Inflammation is typically mild or absent, unlike centrizonal necrosis seen in autoimmune hepatitis or adverse drug reaction.



Ductular Reaction
Ductular reaction → can be seen in portal tracts as well as centrizonal regions. It is generally mild in portal areas but can be prominent and accompanied by portal inflammation &/or focal bile duct damage. These findings can closely mimic biliary disease.

TERMINOLOGY

Abbreviations

- Hepatic venous outflow obstruction (HVOO)

ETIOLOGY/PATHOGENESIS

Venous Obstruction

- Can occur at different levels of hepatic venous outflow
  - Sinusoids or small hepatic veins: Sinusoidal obstruction syndrome (formerly venoocclusive disease)
  - Large hepatic veins or inferior vena cava [Budd-Chiari syndrome (BCS)]
  - Right heart or pericardial disease
    - Right heart failure (either isolated or result of left heart failure)
    - Tricuspid valve disease
    - Cardiac amyloidosis
    - Constrictive pericarditis

Pathogenesis

- Liver changes result from hepatic venous congestion, increased hepatic and sinusoidal pressure, and necrosis
- Secondary sinusoidal thrombosis extending into hepatic and portal veins may contribute to parenchymal damage and fibrosis

CLINICAL ISSUES

Presentation

- Subacute presentation (< 6 months) is most common with painful hepatomegaly, mild jaundice, and ascites
- Less commonly, presents as chronic liver disease or cirrhosis
- Rare cases have fulminant presentation with acute liver failure

Laboratory Tests

- Mild elevation of transaminases; marked increase in acute cases
- Alkaline phosphatase elevation is common

Treatment

- Decompression procedures in BCS
  - Nonsurgical decompression by percutaneous transluminal angioplasty with stent: Suitable for webs or limited stenosis
  - Image-guided transjugular intrahepatic portosystemic shunt
  - Surgical decompression with portosystemic shunt
- For cardiac etiologies, treat underlying disease
- Liver transplant necessary in cases with advanced fibrosis
- Hematological work-up is essential to identify cause of thrombosis

Prognosis

- BCS

- 5-year survival after portosystemic shunt is 75-90%
- 5-year survival after liver transplantation is 60%

- Cardiac disease
  - Depends on type and severity of underlying illness

IMAGING

Radiographic Findings

- For BCS, ultrasound with Doppler flow studies is initial tool of choice
  - Hepatic scintigraphy, CT, and MR can also contribute to diagnosis
  - Hepatic venography was considered gold standard in BCS, but it is now restricted to diagnostically challenging cases
  - Normal hepatic vein flow is not seen
  - Collaterals attempt to decompress obstruction leading to spider web appearance
  - Reverse flow can be seen in portal vein
- For cardiac causes, findings depend on underlying disease

MACROSCOPIC

General Features

- "Nutmeg" liver: Alternating areas of hemorrhagic area and pale parenchyma
- Hemorrhagic areas corresponding to centrizonal areas; pale areas are relatively unaffected periportal parenchyma

MICROSCOPIC

Histologic Features

- Role of liver biopsy: Confirm diagnosis and determine degree of hepatocellular damage
  - Centrizonal-based changes
    – Sinusoidal dilatation and congestion
    – Sinusoidal dilatation compresses hepatocytes leading to hepatic plate atrophy
    – Increased sinusoidal pressure leads to RBC extravasation in space of Disse
    – Hepatocellular necrosis in acute and subacute cases
    – Pericentral and sinusoidal fibrosis in chronic cases that can progress to bridging fibrosis and cirrhosis
    – Fibrosis can be highly variable in distribution, especially in patients with heart failure
  - Portal-based changes
    – Portal expansion with bile ductular reaction with mild lymphoplasmacytic infiltrate
    – Ductular reaction is generally mild but can be florid
    – Bile duct damage can be present in form of lymphocytic cholangitis

– Portal and periportal fibrosis can occur

- Features in certain clinical settings
  - Hyaline eosinophilic deposits in sinusoids &/or vessel walls in amyloidosis
  - Nodular regenerative hyperplasia can be seen
  - Large regenerative nodules in BCS
    - – Can be multiple and range from 0.5-3.5 cm
    - – Presumably result from localized increase in arterial blood flow
    - – Some nodules are associated with ductular reaction resembling focal nodular hyperplasia
    - – Some nodules lack bile ducts resembling hepatic adenoma
- Biopsy features can determine choice of therapy
  - Congestion without significant necrosis or fibrosis
    - – Conservative management with possible repeat biopsy in 3-6 months
  - Congestion with necrosis but no significant fibrosis
    - – Surgical decompression
  - Severe fibrosis or cirrhosis
    - – Liver transplant

DIFFERENTIAL DIAGNOSIS

Other Causes of Sinusoidal Dilatation

- Vascular causes
  - Portal vein thrombosis
  - – Obstruction of portal vein blood flow leads to hepatocyte atrophy
  - – Hepatic atrophy gives appearance of dilated sinusoids

○ Nodular regenerative hyperplasia

– Multiple 0.1- to 0.2-cm nodules without fibrosis

– Occurs in variety of clinical settings, including vascular disorders, myeloproliferative diseases, primary biliary cholangitis

– Nodules compress hepatic microvasculature leading to hepatocyte atrophy and resultant sinusoidal dilatation

- Systemic inflammatory conditions
  - Castleman disease, Crohn disease, rheumatoid arthritis, Still disease, polymyalgia rheumatica
  - Granulomatous conditions, such as sarcoidosis
  - Etiology of sinusoidal dilatation in inflammatory disorders is not clear
- Extrahepatic neoplasms without liver involvement
  - Sinusoidal dilatation is most commonly associated with renal cell carcinoma and Hodgkin lymphoma
  - Other tumors: Carcinomas of stomach, uterus, and colon
- Nonspecific sinusoidal dilatation in different clinical settings
  - Artifactual sinusoidal dilatation
    - – Mechanical reasons, such as rough handling or tearing of biopsy
    - – Often more pronounced at biopsy edges

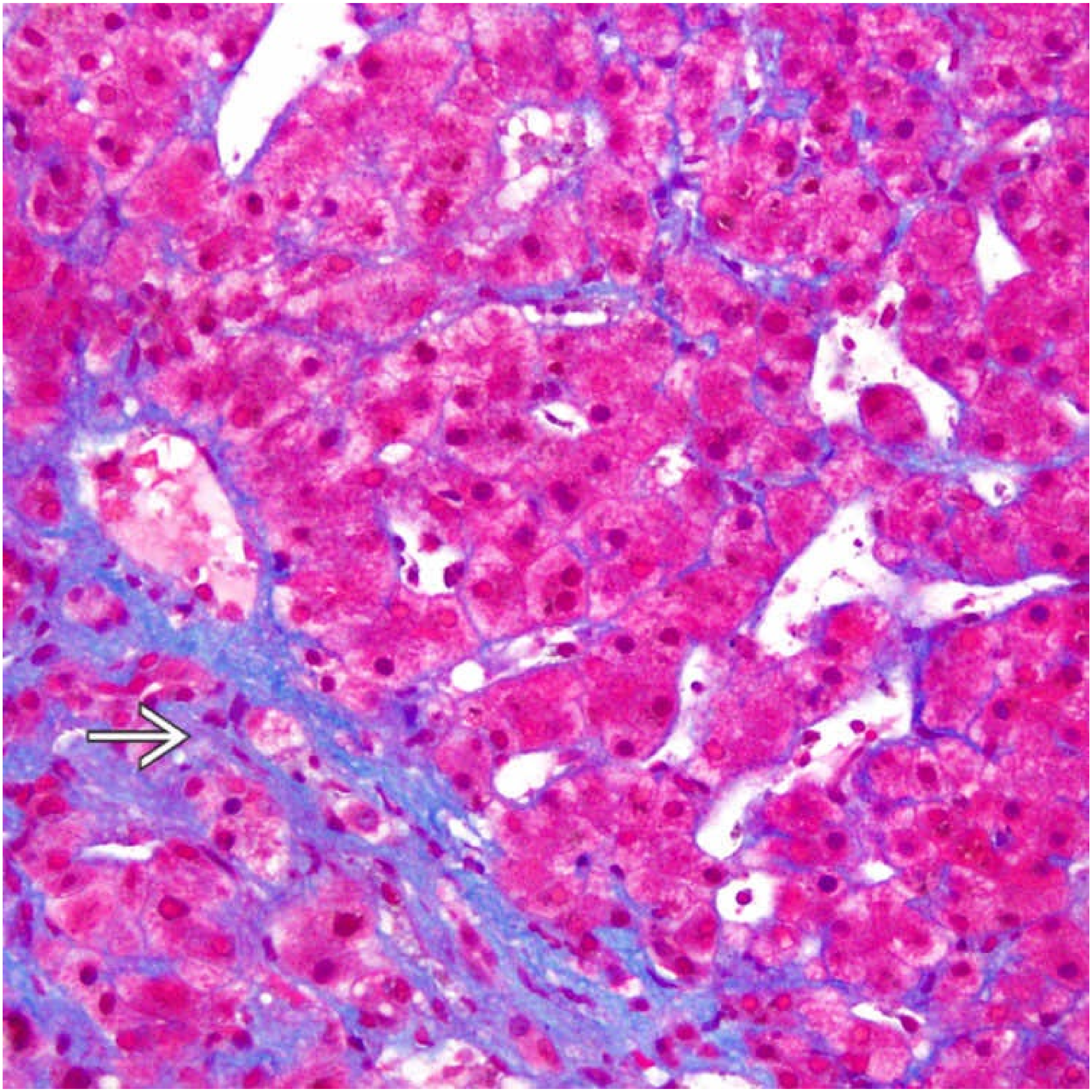
  - Hepatic plate atrophy or extravasation of RBC into space of Disse is not seen
- Transplant liver biopsies
  - Commonly show sinusoidal dilatation in absence of venous outflow obstruction
  - May be related to hemodynamic changes related to vascular anastomosis
- Regenerative nodules in cirrhosis or adjacent to mass lesions
  - Can lead to adjacent sinusoidal dilatation due to localized venous outflow obstruction
- Intraoperative biopsies
  - Sinusoidal dilatation is common in biopsies obtained during abdominal surgeries
  - May be due to alterations in portal blood flow during abdominal surgery

Biliary Disease

- Portal changes, such as ductular reaction and lymphocytic inflammation, can occur in HVOO
- Elevation of alkaline phosphatase is also common
- Both of these features can lead to additional suspicion of biliary disease, such as bile duct obstruction or primary biliary cholangitis
- Normal bile ducts on imaging and negative antimitochondrial antibodies do not support biliary disease

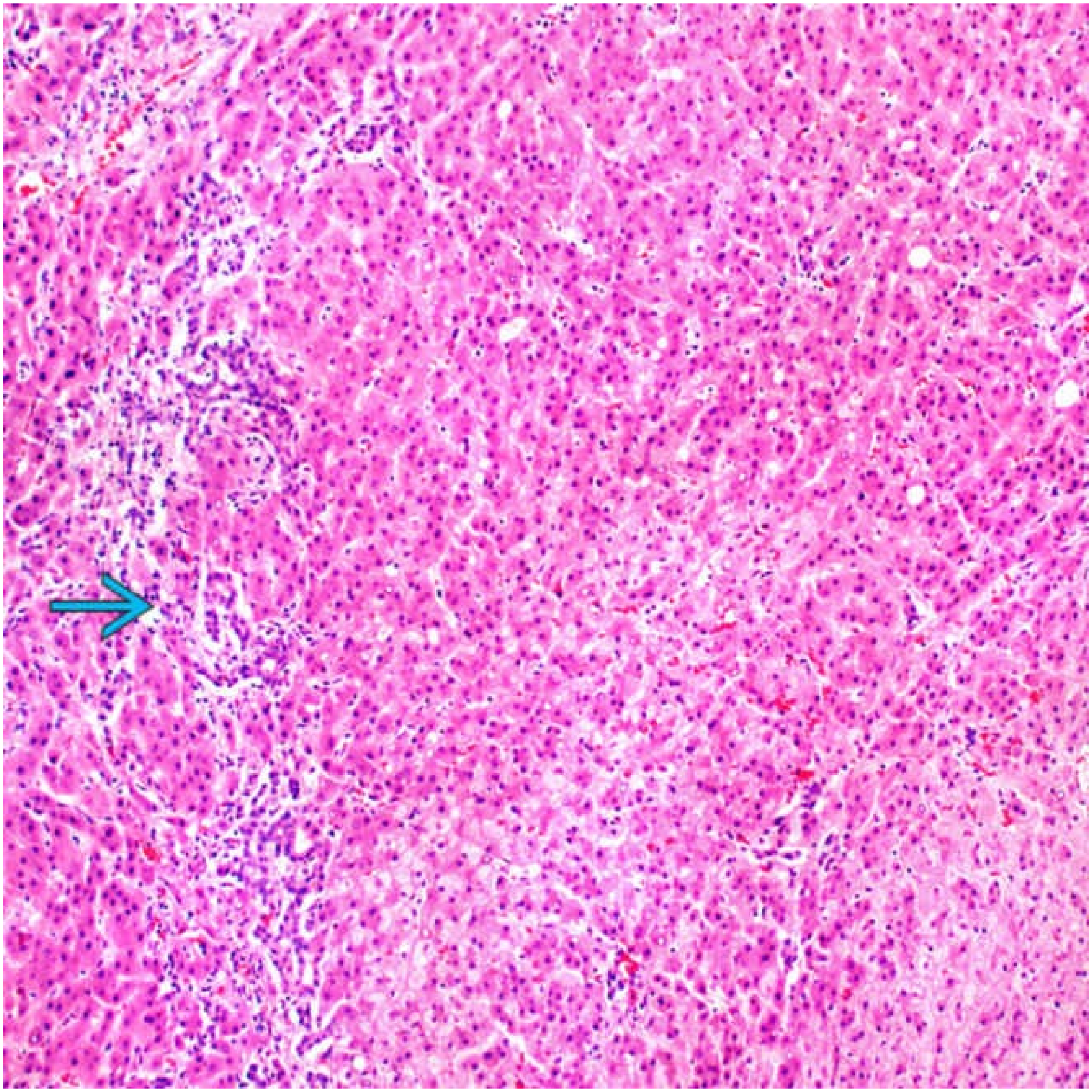
Other Causes of Parenchymal Necrosis/Hemorrhage

- Acetaminophen toxicity
  - Centrizonal necrosis and absence of inflammation mimics venous outflow obstruction
  - Sinusoidal dilatation may be focal but is not marked
  - Drug history and acetaminophen levels point toward correct diagnosis
- Ischemic liver injury
  - Centrizonal hemorrhage, necrosis, and absence of inflammation mimics venous outflow obstruction
  - Prominent sinusoidal dilatation is usually not present
  - History of cardiogenic or noncardiogenic (septic, hypovolemic) shock, heatstroke is key to diagnosis
- Wilson disease
  - Necrosis without prominent inflammation can be seen
  - Typical features of venous outflow obstruction, such as sinusoidal dilatation and congestion, are not seen
  - Copper studies will lead to correct diagnosis
- Viral hepatitis
  - Herpes simplex and adenoviral hepatitis can lead to hemorrhagic necrosis without significant inflammation
  - Viral inclusions confirmed by immunohistochemistry establish diagnosis

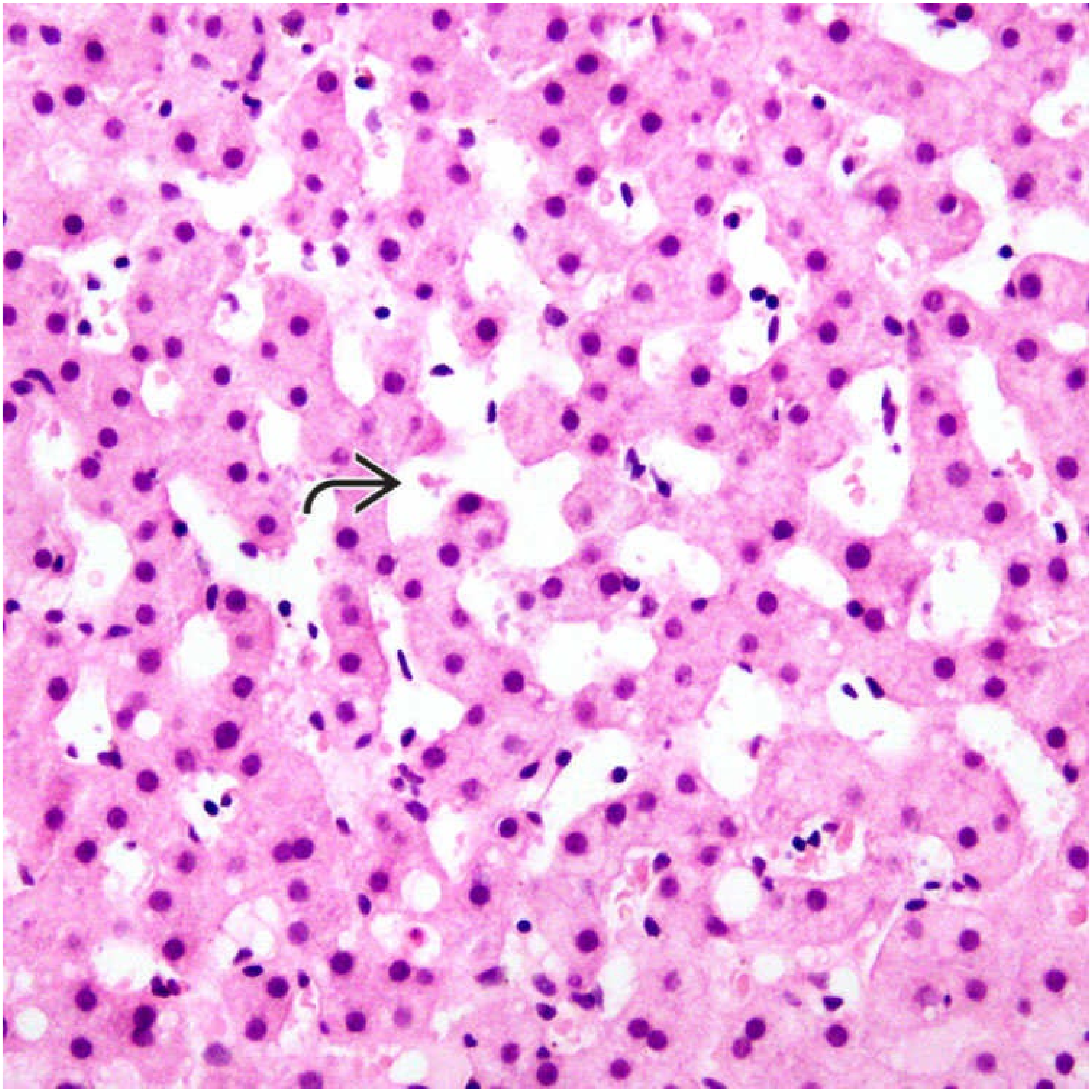


Perivenular Fibrosis

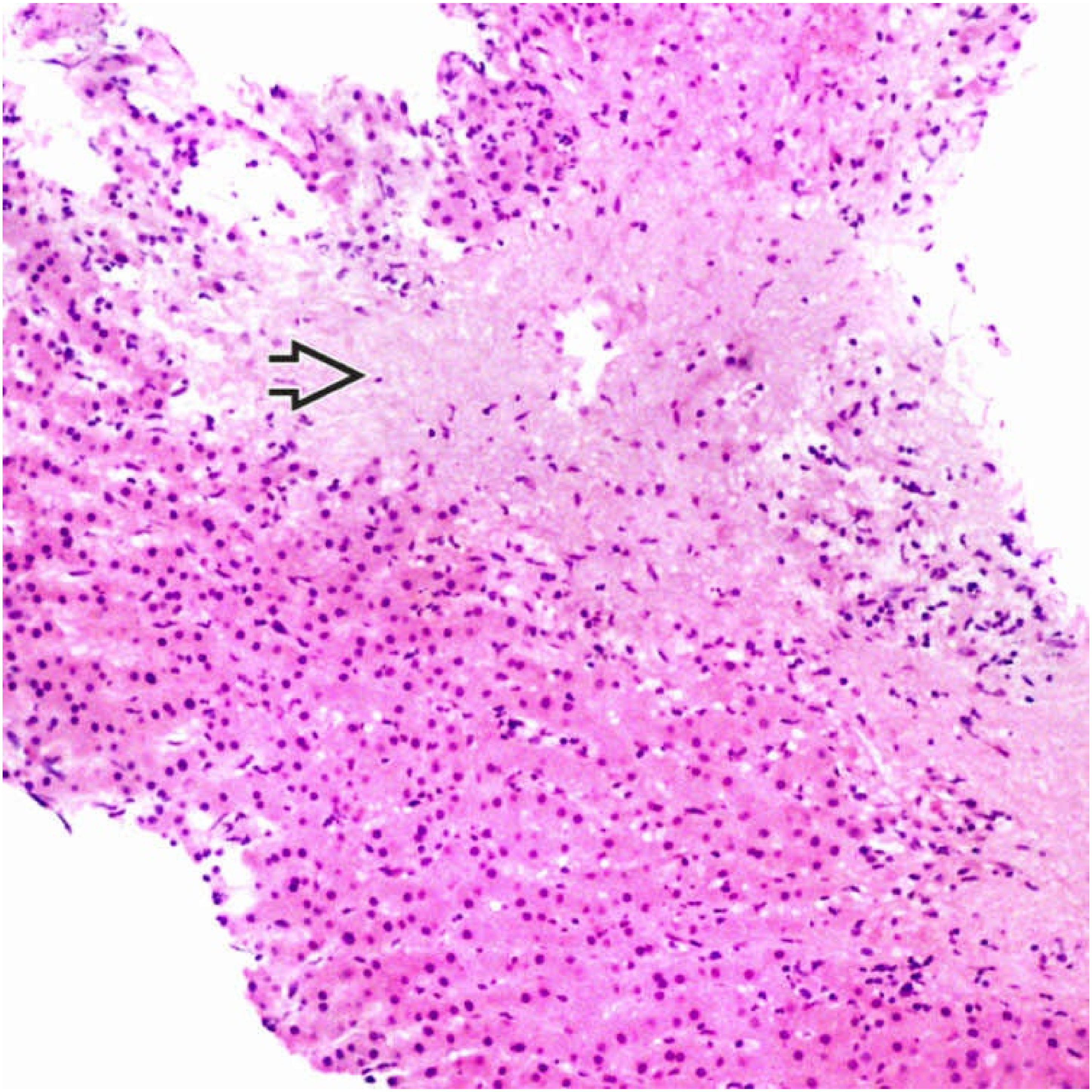
Fibrosis around the central vein can occur in a pericellular fashion in chronic cases. The fibrosis can progress to cirrhosis (cardiac cirrhosis).



FNH-Like Nodule
Large regenerative nodules in Budd-Chiari syndrome can histologically resemble focal nodular hyperplasia or adenoma. The thin septum with ductular reaction → in this case is reminiscent of focal nodular hyperplasia (FNH).

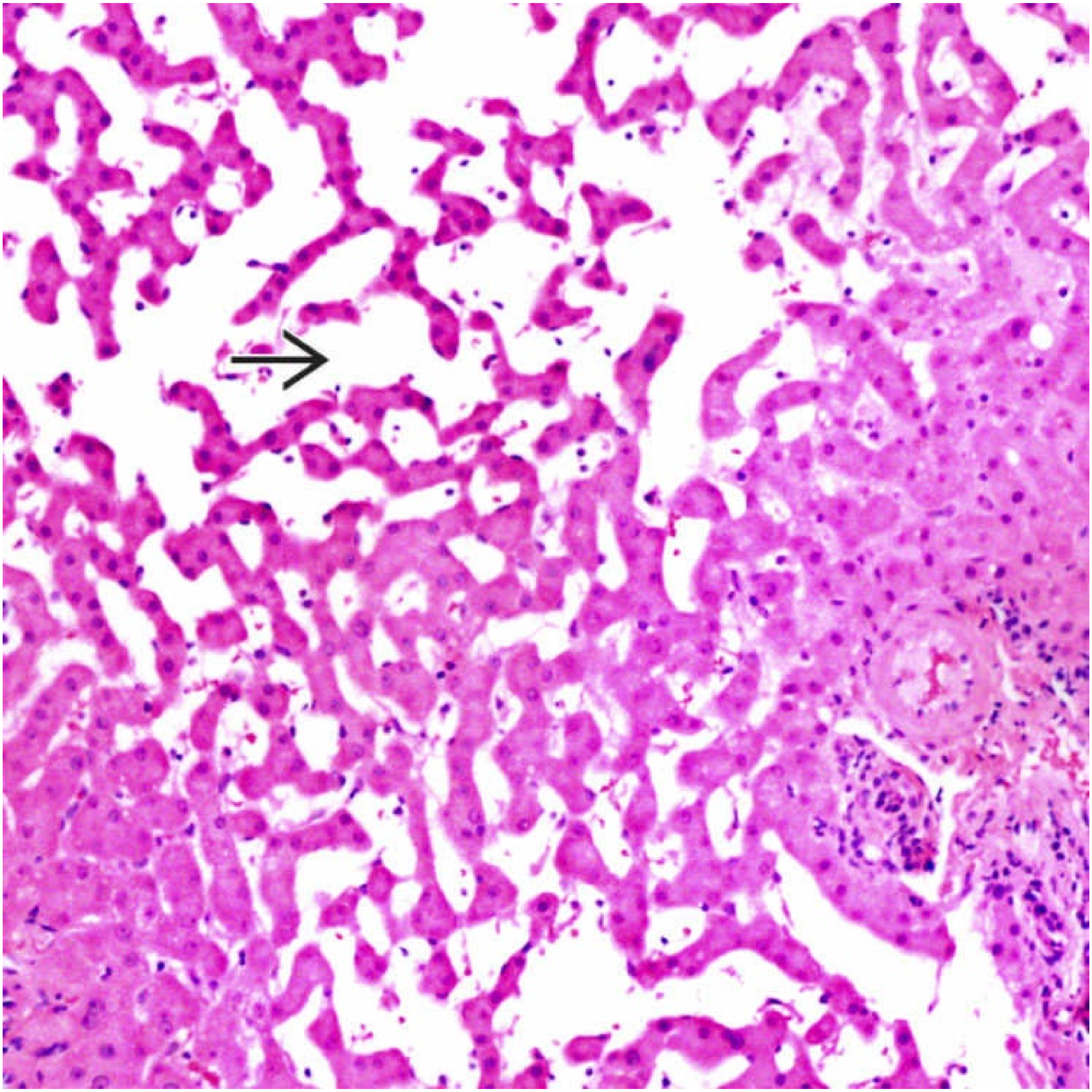


Sinusoidal Dilatation Without Atrophy
Artifactual sinusoidal dilatation can be distinguished from hepatic venous outflow obstruction by the lack of centrizonal distribution, hepatic plate atrophy, and RBC extravasation.

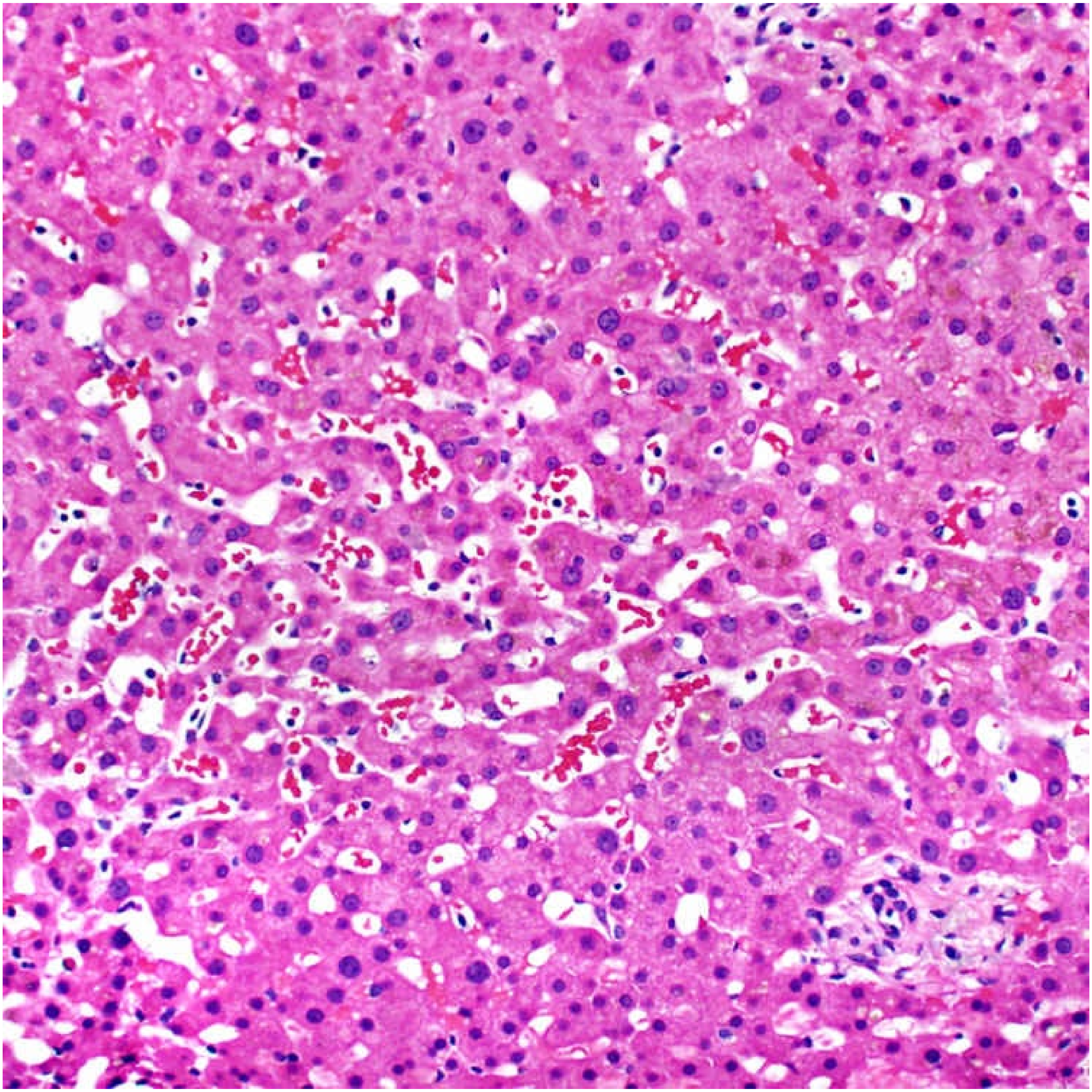


Necrosis Without Sinusoidal Dilatation

Centrizonal necrosis ➩ without significant inflammation is seen in a case of hepatic ischemia. The sinusoidal dilatation is not prominent. This condition can closely mimic venous outflow obstruction.



Marked Sinusoidal Dilatation
Marked dilatation of sinusoids → and hepatic plate atrophy are seen in a case of Castleman disease. These features can occur in systemic inflammatory conditions and can mimic venous outflow obstruction.



Sinusoidal Dilatation After Chemotherapy
Sinusoidal injury as a result of chemotherapy can result in sinusoidal dilatation, congestion, and plate atrophy mimicking venous outflow obstruction. This is typically seen following bone marrow transplantation and with drugs like oxaliplatin used for liver metastasis from colorectal cancer.

SELECTED REFERENCES

1. Louie, CY, et al. The liver in heart failure: a biopsy and explant series of the histopathologic and laboratory findings with a particular focus on pre-cardiac transplant evaluation. *Mod Pathol*. 2015; 28(7):932–943.
2. Sempoux, C, et al. Hepatocellular nodules expressing markers of hepatocellular adenomas in Budd-Chiari syndrome and other rare hepatic vascular disorders. *J Hepatol*. 2015; 63(5):1173–1180.

3. Ibarrola, C, et al. Focal hyperplastic hepatocellular nodules in hepatic venous outflow obstruction: a clinicopathological study of four patients and 24 nodules. *Histopathology*. 2004; 44(2):172–179.
4. Kakar, S, et al. Histologic changes mimicking biliary disease in liver biopsies with venous outflow impairment. *Mod Pathol*. 2004; 17(7):874–878.
5. Kakar, S, et al. Sinusoidal dilatation and congestion in liver biopsy: is it always due to venous outflow impairment? *Arch Pathol Lab Med*. 2004; 128(8):901–904.
6. Tanaka, M, et al. Pathology of the liver in Budd-Chiari syndrome: portal vein thrombosis and the histogenesis of veno-centric cirrhosis, veno-portal cirrhosis, and large regenerative nodules. *Hepatology*. 1998; 27(2):488–496.
7. Wanless, IR, et al. Role of thrombosis in the pathogenesis of congestive hepatic fibrosis (cardiac cirrhosis). *Hepatology*. 1995; 21(5):1232–1237.
8. Dilawari, JB, et al. Hepatic outflow obstruction (Budd-Chiari syndrome). Experience with 177 patients and a review of the literature. *Medicine (Baltimore)*. 1994; 73(1):21–36.
9. Bruguera, M, et al. Incidence and clinical significance of sinusoidal dilatation in liver biopsies. *Gastroenterology*. 1978; 75(3):474–478.
10. Poulsen, H, et al. The significance of centrilobular sinusoidal changes in liver biopsies. *Scand J Gastroenterol Suppl*. 1970; 7:103–109.

Venoocclusive Disease

KEY FACTS

Terminology

- Term sinusoidal obstruction syndrome has been recently advocated

Etiology/Pathogenesis

- Stem cell transplantation and high-dose chemotherapy
- Sinusoidal endothelial cell injury is important initial event
- Herbal medicines containing pyrrolizidine alkaloids, rarely liver transplant
- Rare causes of sinusoidal obstruction: Sickle cell crisis, *Plasmodium falciparum* malaria, extensive infiltration by neoplastic cells

Clinical Issues

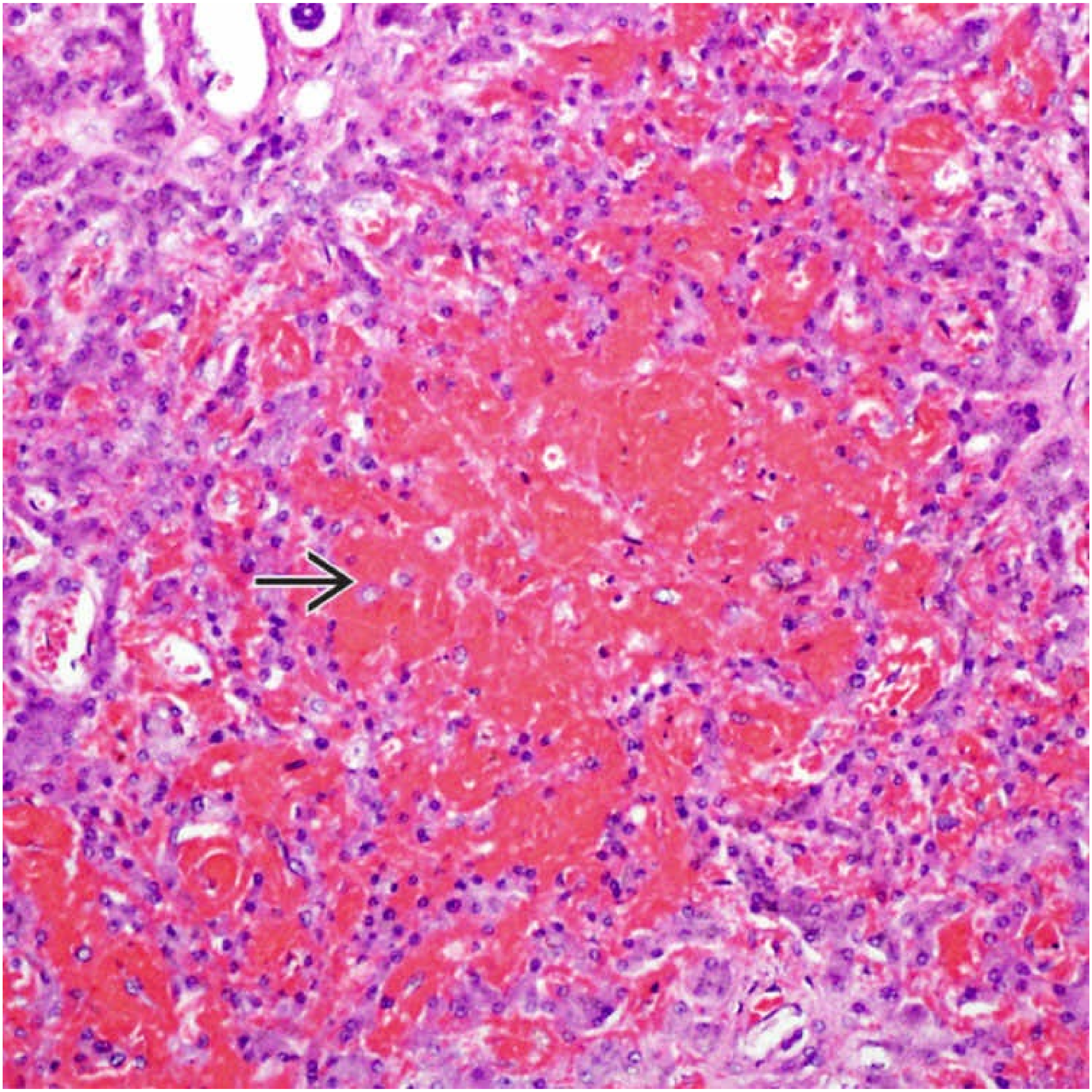
- Hyperbilirubinemia, weight gain, and painful hepatomegaly
- Attenuated or reverse flow in portal vein on Doppler ultrasound
- Outcome depends on disease severity with high mortality in severe disease
- Adverse prognostic factors: Ascites, multiorgan failure, WHVPG > 20 mmHg

Microscopic

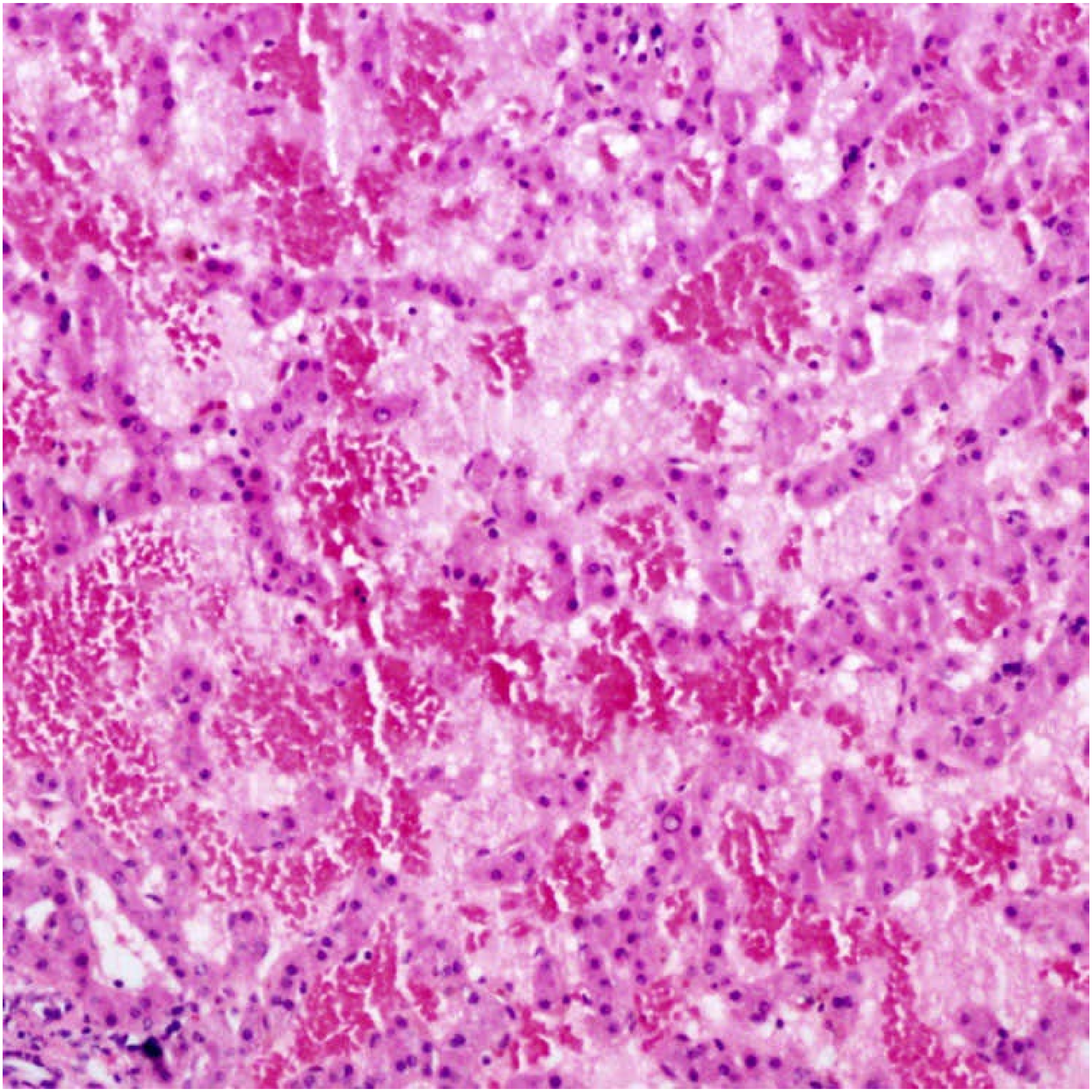
- Subendothelial edema, red cell extravasation, fibrin deposition in sinusoids and central vein
- Zone 3 sinusoidal dilatation and hepatocellular necrosis
- Venular obliteration and widespread fibrosis
- Changes can be patchy in early disease leading to false-negative results
- Fibrosis develops in sinusoids and venular wall

Top Differential Diagnoses

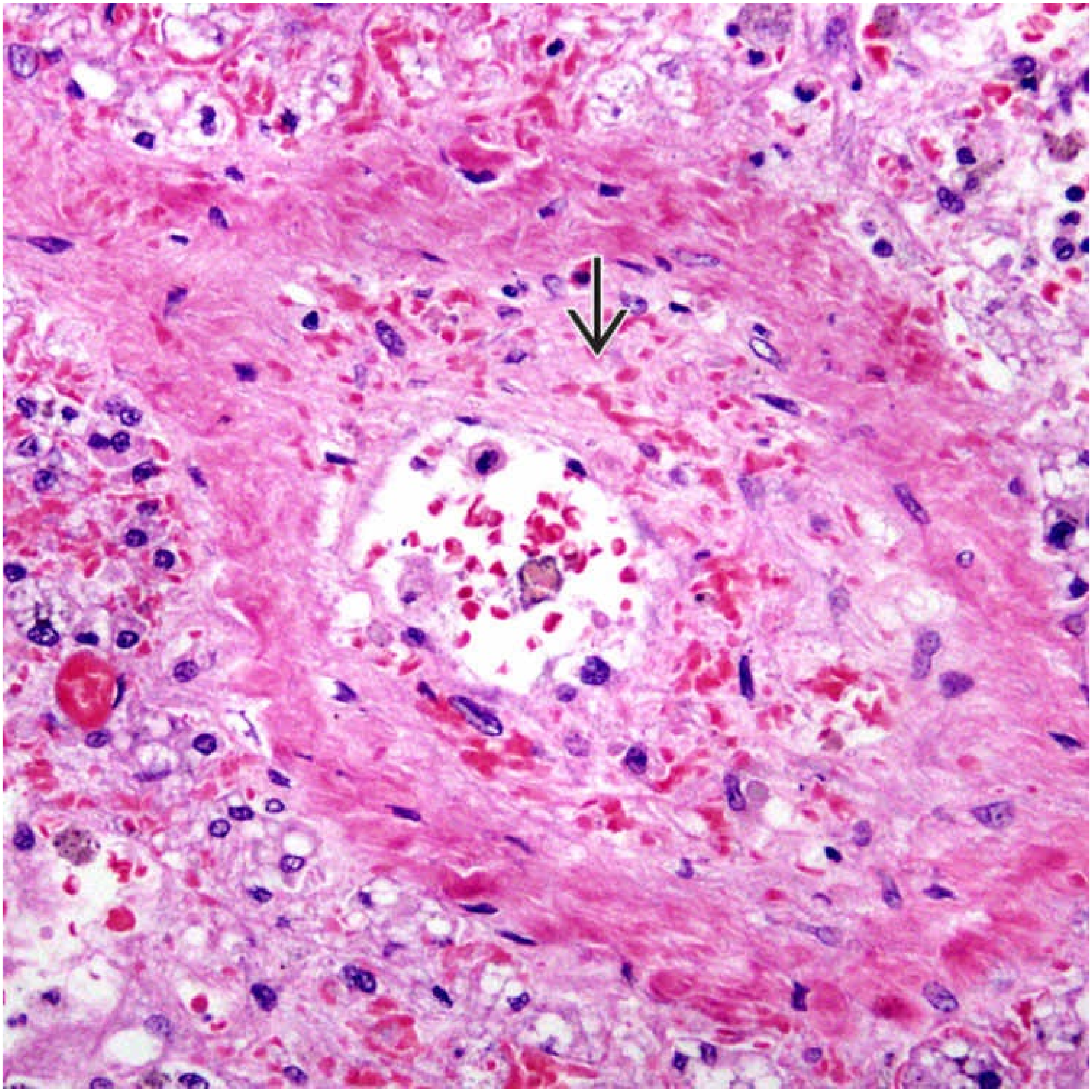
- Acute graft-vs.-host disease
- Hepatic venous outflow obstruction



Marked Congestion
In severe cases, venoocclusive disease is characterized by marked congestion in the sinusoids and can be accompanied by areas of hemorrhage →.

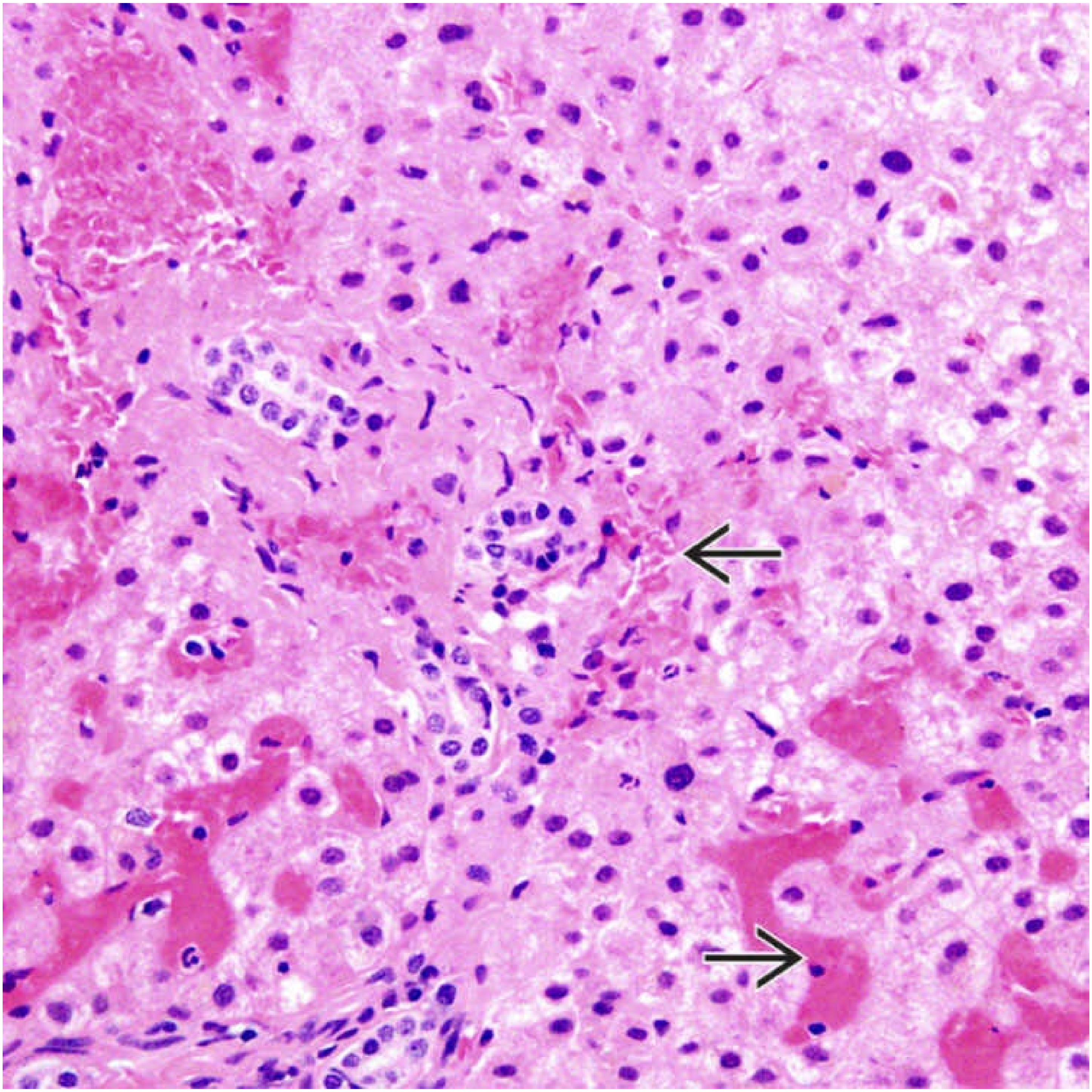


Congestion and Plate Atrophy
Endothelial injury in sinusoids and small hepatic veins leads to venous outflow obstruction that manifests as sinusoidal dilatation, congestion, and hepatic plate atrophy.



Venous Occlusion

Endothelial swelling with subendothelial edema and fibrosis → leads to partial occlusion of the lumen of a small hepatic vein in venoocclusive disease. These characteristic lesions may not be evident in biopsies.



Sickle Cell Crisis
Sinusoidal obstruction caused by occlusion of hepatic sinusoids by sickled red blood cells → in hepatic sickle cell crisis is shown. This is a rare phenomenon but can cause sinusoidal obstruction syndrome and present in an acute fashion.

TERMINOLOGY

Abbreviations

- Venoocclusive disease (VOD)

Synonyms

- Sinusoidal obstruction syndrome (SOS)

ETIOLOGY/PATHOGENESIS

Etiology

- Stem cell transplantation and high-dose chemotherapy
- Herbal medicines containing pyrrolizidine alkaloids
- Rare complication of liver transplantation
- Rare causes of sinusoidal obstruction: Sickle cell crisis, *Plasmodium falciparum* malaria, extensive infiltration by neoplastic cells

Risk Factors

- Older age and poor performance status
- HLA disparity in allogeneic stem cell transplant
- Preexisting liver dysfunction
- Prior abdominal radiation
- Pretransplant use of acyclovir or vancomycin
- High-dose busulphan and cyclophosphamide therapy

Pathogenesis

- Injury to sinusoidal endothelial cells is important initial event; hence, preferred term is SOS
- Major damage occurs in zone 3, which has high concentration of cytochrome P450 enzymes that metabolize many chemotherapeutic agents
- Depletion of glutathione, also predominantly present in centrizonal location, plays role in hepatocyte necrosis

CLINICAL ISSUES

Presentation

- SOS in stem cell transplantation
  - Typically occurs in 1st 3 weeks
  - Triad of hyperbilirubinemia, weight gain, and painful hepatomegaly
  - Plasma levels of plasminogen activator inhibitor-1 are often elevated
  - Attenuated or reverse flow in portal vein on Doppler ultrasound
  - Wedged hepatic venous pressure gradient (WHVPG) > 10 mmHg has 91% specificity and 52% sensitivity
  - Diagnosis often based on clinical criteria, biopsy reserved for unclear cases

Treatment

- Use of pharmacokinetics to monitor drug levels with intent of minimizing hepatic injury
- Fibrinolytic agents such as recombinant tissue plasminogen activator and anticoagulants like heparin
- Antiinflammatory agents such as ursodiol and pentoxifylline
- Endothelial protective agents such as prostaglandin E1 and defibrotide

- Glutathione and N-acetyl cysteine supplementation

Prognosis

- Mild disease: No significant adverse effect from liver dysfunction with complete resolution
- Moderate disease: Requiring therapy but with eventual complete resolution
- Severe: Dismal outcome, mortality approaching 100%
- Adverse prognostic factors: Ascites, multiorgan failure, WHVPG > 20 mmHg

MICROSCOPIC

Histologic Features

- Liver biopsy is done through transjugular route; percutaneous biopsy is contraindicated given high risk for bleeding
- Changes can be patchy in early disease leading to false-negative results
- Subendothelial edema, red cell extravasation, fibrin deposition in central vein and sinusoids
- Narrowing of venular lumen leads to sinusoidal dilatation and hepatocyte necrosis
- Fibrosis develops in sinusoids and venular wall
- Eventually leads to venular obliteration, extensive hepatocellular necrosis, and widespread fibrosis

DIFFERENTIAL DIAGNOSIS

Acute Graft-vs.-Host Disease

- Also causes acute liver dysfunction after stem cell transplant
- Bile duct damage and apoptosis are not seen in VOD
- Centrizonal hepatocellular damage is not characteristic of GVHD

Hepatic Venous Outflow Obstruction

- Venular luminal compromise, obliteration absent in hepatic venous outflow obstruction

SELECTED REFERENCES

1. Palladino, M, et al. Severe veno-occlusive disease after autologous peripheral blood stem cell transplantation for high-grade non-Hodgkin lymphoma: report of a successfully managed case and a literature review of veno-occlusive disease. *Clin Transplant*. 2008; 22(6):837–841.
2. Karoui, M, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. *Ann Surg*. 2006; 243(1):1–7.
3. Kumar, S, et al. Hepatic veno-occlusive disease (sinusoidal obstruction syndrome) after hematopoietic stem cell transplantation. *Mayo Clin Proc*. 2003; 78(5):589–598.
4. Wadleigh, M, et al. Hepatic veno-occlusive disease: pathogenesis, diagnosis and treatment. *Curr Opin Hematol*. 2003; 10(6):451–462.
5. Dhillon, AP, et al. Hepatic venular stenosis after orthotopic liver transplantation. *Hepatology*.

1994; 19(1):106–111.

Amyloidosis

KEY FACTS

Etiology/Pathogenesis

- Liver involvement most common in AL and LECT2 amyloidosis
- AA and hereditary amyloidosis can also involve liver

Microscopic

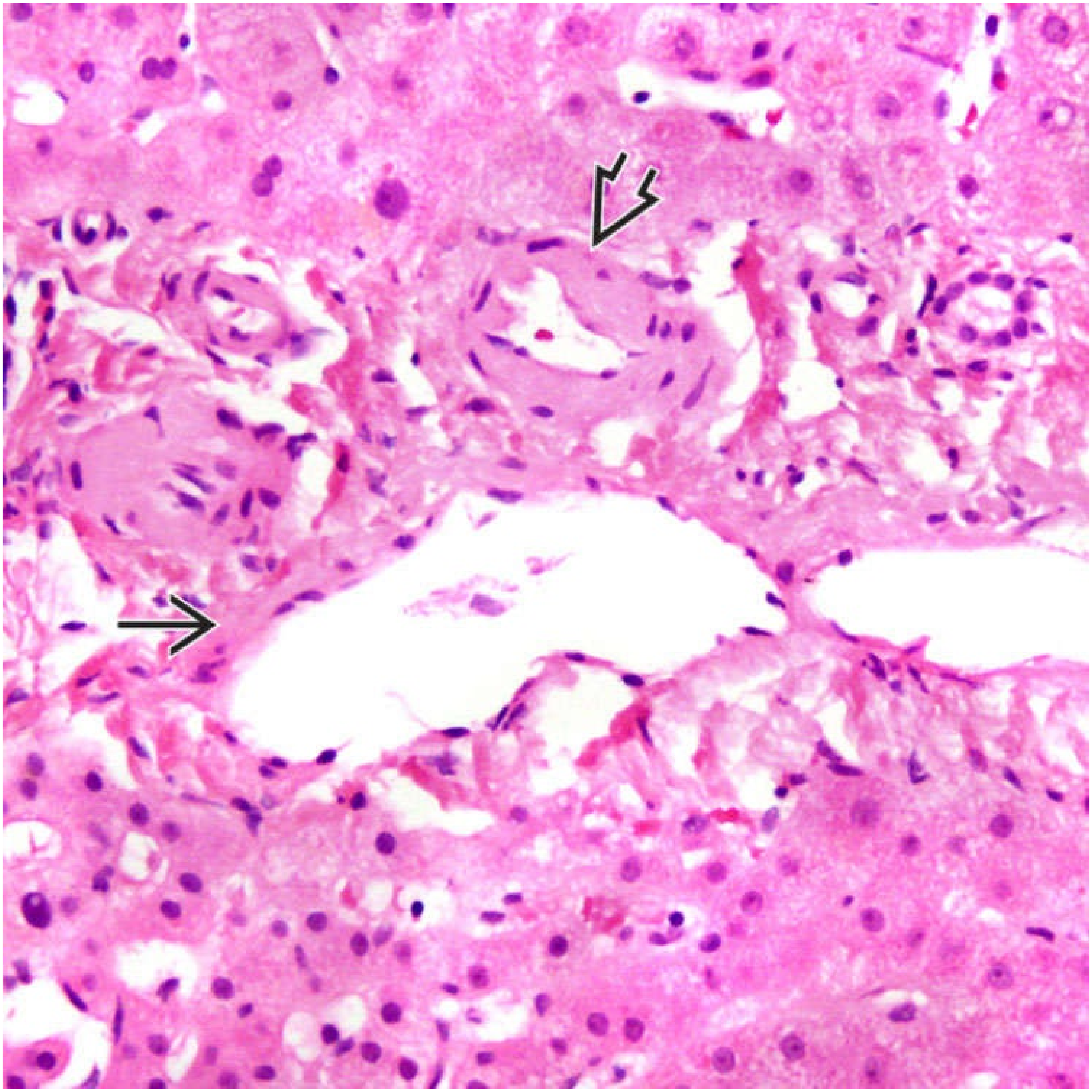
- Sinusoidal pattern is more common in AL amyloidosis and vascular pattern in AA amyloidosis
  - Distribution patterns show overlap and are not reliable for definite distinction between AL and AA amyloidosis
  - Globular pattern of deposition is typical of LECT2 amyloidosis
  - Congo red stain
    - Amyloid deposits are congophilic and show “apple green” birefringence under polarized light
    - Birefringence is best demonstrated by turning light to maximum and pulling color filters out
- Immunohistochemistry
  - P glycoprotein: Present in all cases, can help in diagnosis
  - Light chains, SAA, and LECT2: Helps in further classification

Ancillary Tests

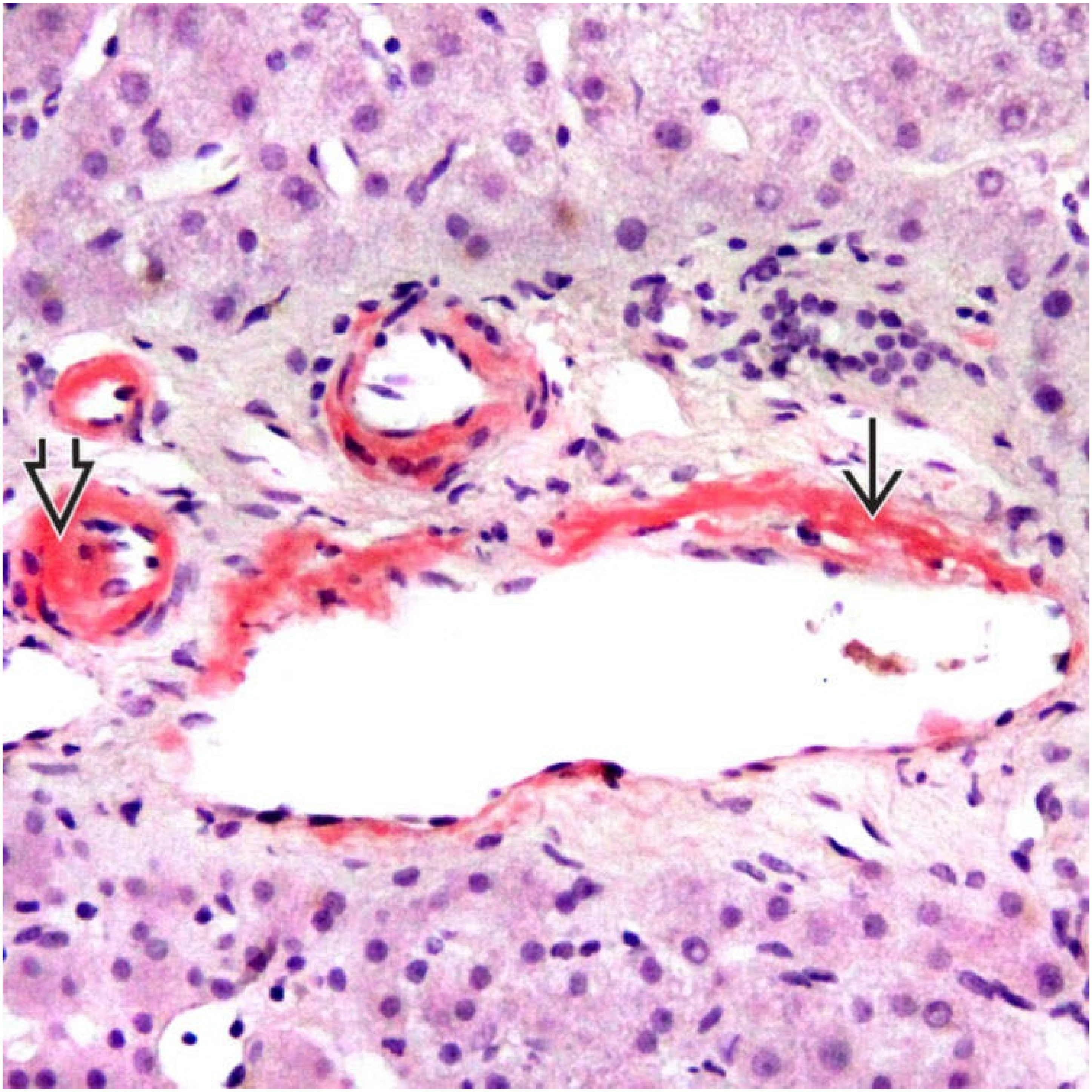
- Electron microscopy
  - Central electron-lucent core and nonbranching fibrils of indefinite length with mean diameter of 10 nm
- Laser microdissection and mass spectrometry
  - Most accurate method for identification of amyloid subtype
  - Paraffin-embedded tissue or cytology material can be used

Top Differential Diagnoses

- Monoclonal immunoglobulin deposit disease

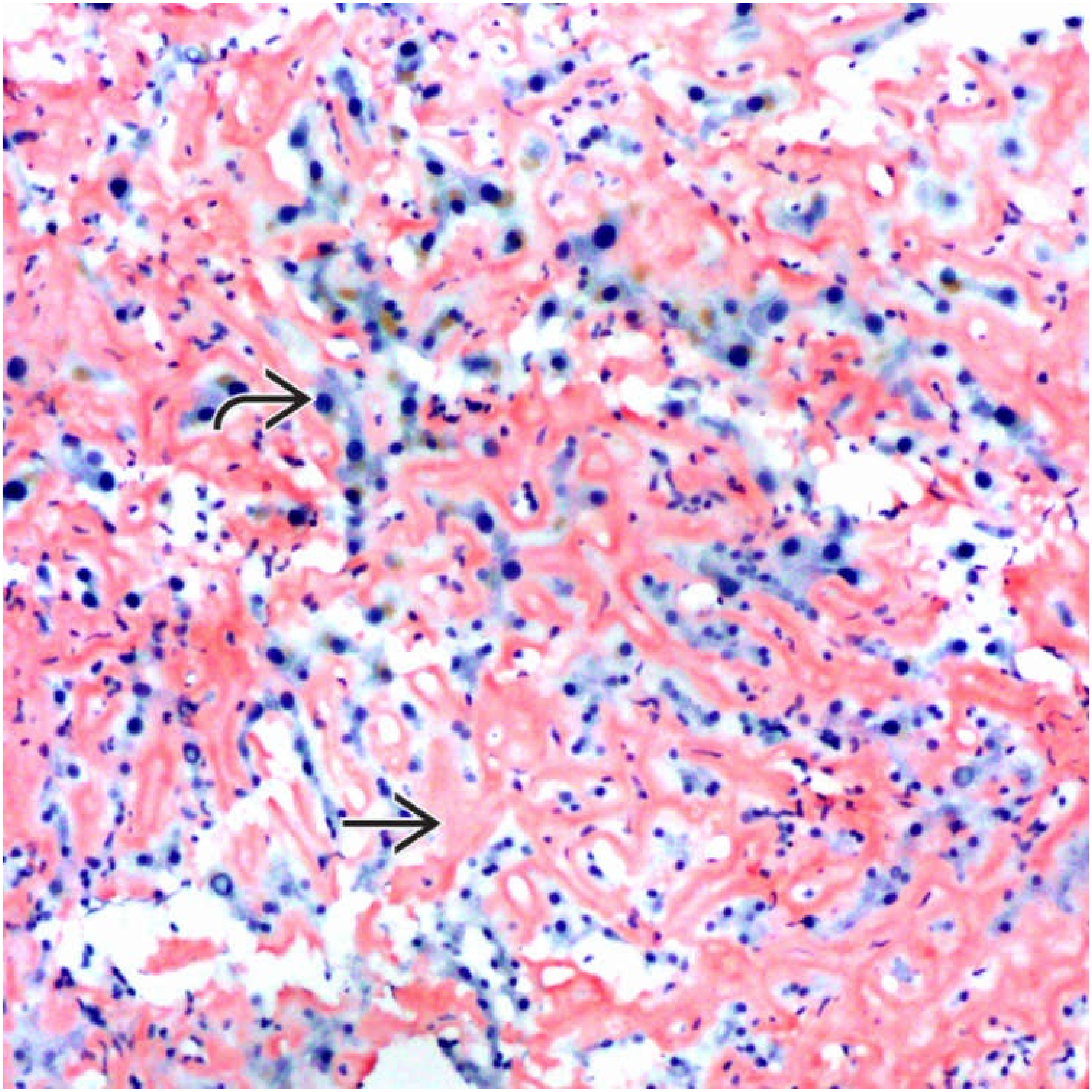


Vessel Wall Amyloid
Deposits are seen in the hepatic arteriole ⇨ and portal vein → in the vascular pattern of hepatic amyloidosis. This distribution is characteristic, but not specific, for the AA form.



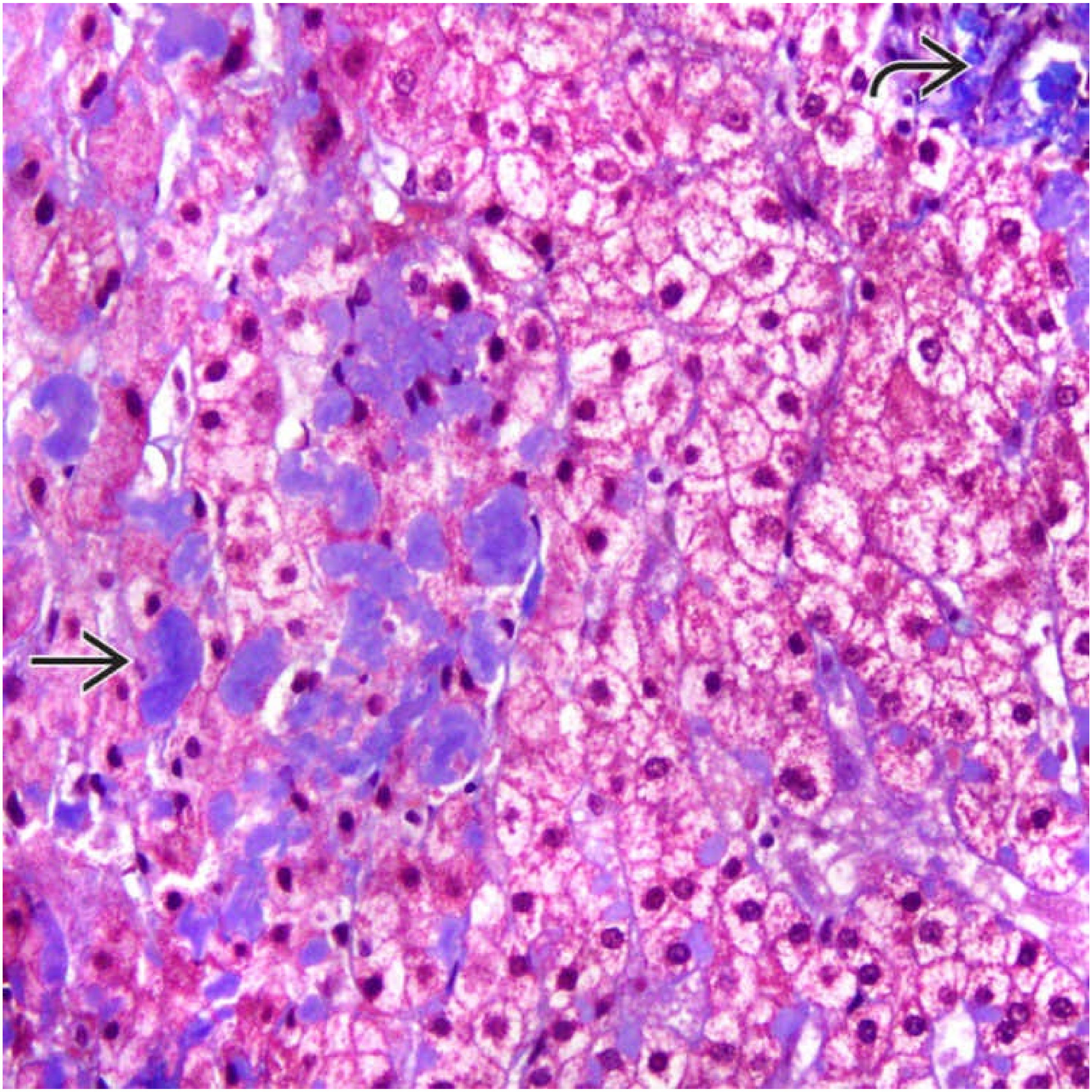
Congo Red Stain

Congo red stain highlights the vascular distribution of amyloid deposits in the hepatic arteriole ⇨ and portal vein →.



Sinusoidal Amyloid

Congo red stain highlights the diffuse sinusoidal pattern → of hepatic amyloidosis. The amyloid deposits are compressing the hepatocytes ↱, leading to hepatic plate atrophy.



Globular Amyloid
Amyloid deposits → stain with trichrome stain, but it is often a paler staining than that seen with collagen ↱.

TERMINOLOGY

Definitions

- Heterogeneous disease characterized by deposition of glycoprotein fibrils in extracellular matrix and vessel walls
  - Deposits composed of low molecular weight subunits (5-25 KDa) derived from normal serum proteins
- Liver involvement may be seen in different types

- Primary, or AL, amyloidosis
  - Deposits are composed of fragments of monoclonal light chains
  - Occurs alone or associated with other hematologic diseases (plasmacytoma, multiple myeloma Waldenstrom macroglobulinemia)
  - Liver involved in up to 70% of cases
  - Hepatic involvement reflects advanced disease and denotes poor prognosis
- Secondary, or AA, amyloidosis
  - Deposits are composed of fragments of SAA protein, acute phase reactant
  - Often secondary to chronic infections, systemic diseases, such as rheumatoid arthritis
- Hereditary amyloidosis
  - Hereditary AApoAI amyloidosis: Some mutations in apolipoprotein A1 can lead to hepatic amyloidosis
- LECT2 amyloidosis
  - Deposition of LECT2 protein
  - Accounts for 25% of hepatic cases

CLINICAL ISSUES

Presentation

- May be asymptomatic
- More common in men; mean age: 60 years
- Common symptoms: Weight loss, fatigue, abdominal pain, anorexia, early satiety, nausea, dysgeusia
- Physical exam: Hepatomegaly, ascites, edema, purpura, splenomegaly
- Extrahepatic manifestations often present

Laboratory Tests

- Elevated alkaline phosphatase (often > 500 IU/L)
- Mild elevation of liver transaminases occurs in 1/3 of cases

Treatment

- High-dose chemotherapy, autologous stem cell transplantation for AL amyloidosis
- Liver transplant for some hereditary cases

Prognosis

- Generally poor
- Elevated bilirubin and congestive heart failure are adverse prognostic factors

MICROSCOPIC

Histologic Features

- Amyloid deposition in sinusoids &/or vessel walls
  - Sinusoidal pattern more common in AL amyloidosis, vascular pattern in AA
  - Distribution patterns overlap and are not reliable for definite distinction between AL and AA amyloidosis
- Globular deposits in sinusoids typical of LECT2 amyloidosis
- Macrophages, multinucleated giant cells around amyloid deposits
- Mild portal fibrosis can occur, no advanced fibrosis
- Congo red stain is gold standard for diagnosis
  - Congophilic deposits with “apple green” birefringence under polarized light
    - Color varies from yellow-green to blue-green, changes with rotation of polarizer/analyzer
    - Different areas can demonstrate different colors
    - Birefringence is best demonstrated by turning light to maximum and pulling color filters out
    - Thick sections (10 μm) can increase sensitivity
    - Congophilia can be reduced after prolonged fixation
  - Fluorescence microscopy using fluorescein isothiocyanate filter yields yellow fluorescence with Congo red but is not specific for amyloid
- Immunohistochemistry
  - Glycoprotein P component can help in diagnosis, present in all amyloid deposits
  - Light chains (AL type), SAA (AA type), LECT2 can help to subtype amyloid deposits
  - Background staining can make interpretation difficult

ANCILLARY TESTS

Electron Microscopy

- Central electron-lucent core and nonbranching fibrils of indefinite length with mean diameter of 10 nm

Laser Microdissection and Mass Spectrometry

- Most accurate method for identification of amyloid subtype
- Paraffin-embedded tissue or cytology material can be used

DIFFERENTIAL DIAGNOSIS

Monoclonal Immunoglobulin Deposit Disease

- Deposition of monoclonal protein (M protein) in tissue
- AL amyloidosis is form of monoclonal immunoglobulin deposit disease (distinguished from other forms by Congo red staining)
- Other forms: Light chain deposition disease, heavy chain deposition disease, light and heavy chain deposition disease

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Diagnosis should be suspected in setting of involuntary weight loss, hepatomegaly, unexplained elevated serum alkaline phosphatase level, proteinuria, or evidence for hyposplenism

SELECTED REFERENCES

1. Chandan, VS, et al. Globular hepatic amyloid Is highly sensitive and specific for LECT2 amyloidosis. *Am J Surg Pathol*. 2015; 39(4):558–564.
2. Howie, AJ, et al. Optical properties of amyloid stained by Congo red: history and mechanisms. *Micron*. 2009; 40(3):285–301.
3. Malnick, S, et al. The involvement of the liver in systemic diseases. *J Clin Gastroenterol*. 2008; 42(1):69–80.
4. Park, MA, et al. Primary (AL) hepatic amyloidosis: clinical features and natural history in 98 patients. *Medicine (Baltimore)*. 2003; 82(5):291–298.
5. Gertz, MA, et al. Hepatic amyloidosis: clinical appraisal in 77 patients. *Hepatology*. 1997; 25(1):118–121.
6. Buck, FS, et al. Hepatic amyloidosis: morphologic differences between systemic AL and AA types. *Hum Pathol*. 1991; 22(9):904–907.
7. Chopra, S, et al. Hepatic amyloidosis. A histopathologic analysis of primary (AL) and secondary (AA) forms. *Am J Pathol*. 1984; 115(2):186–193.

Ischemia

KEY FACTS

Terminology

• Ischemic hepatitis, hepatic infarction, and shock liver
• Liver injury due to reduced blood flow

Etiology/Pathogenesis

• Cardiac failure
• Circulatory shock due to sepsis, hypovolemia, severe trauma, burns, and other causes
• Vascular thromboses due to stasis, endothelial injury, and hypercoagulable state
• In transplant patients, anastomotic complications

Clinical Issues

• Often asymptomatic
• Characterized by rapid and extreme rise in serum aminotransferases
• Patients may develop acute liver failure

Microscopic

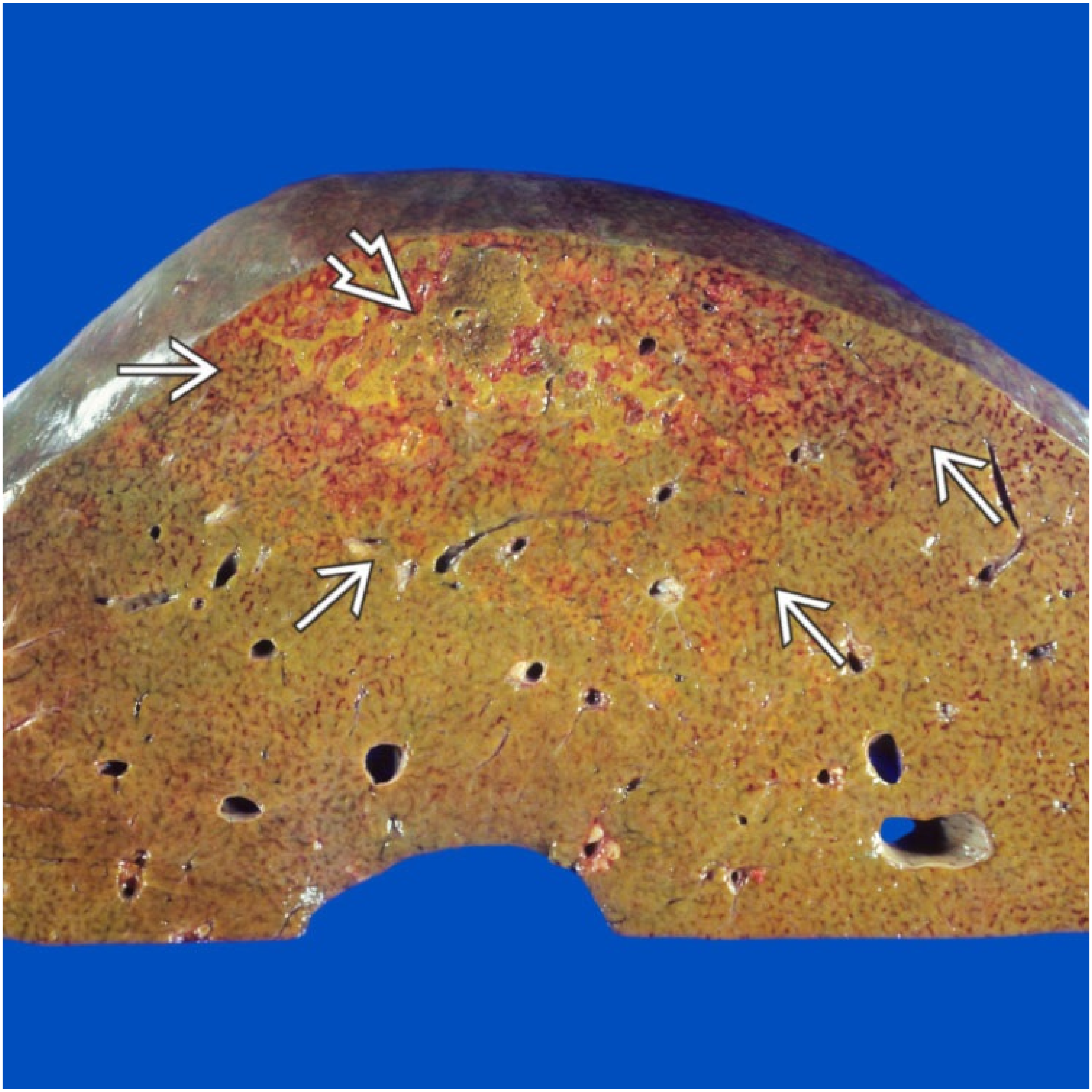
• Range of findings, depending on location and extent of ischemic insult
• Sharply demarcated zones of coagulative hepatocyte necrosis
• Minimal inflammation

Top Differential Diagnoses

• Infection
  ○ Causes nonzonal or “geographic” necrosis
• Drug-induced liver injury
• Chronic passive congestion

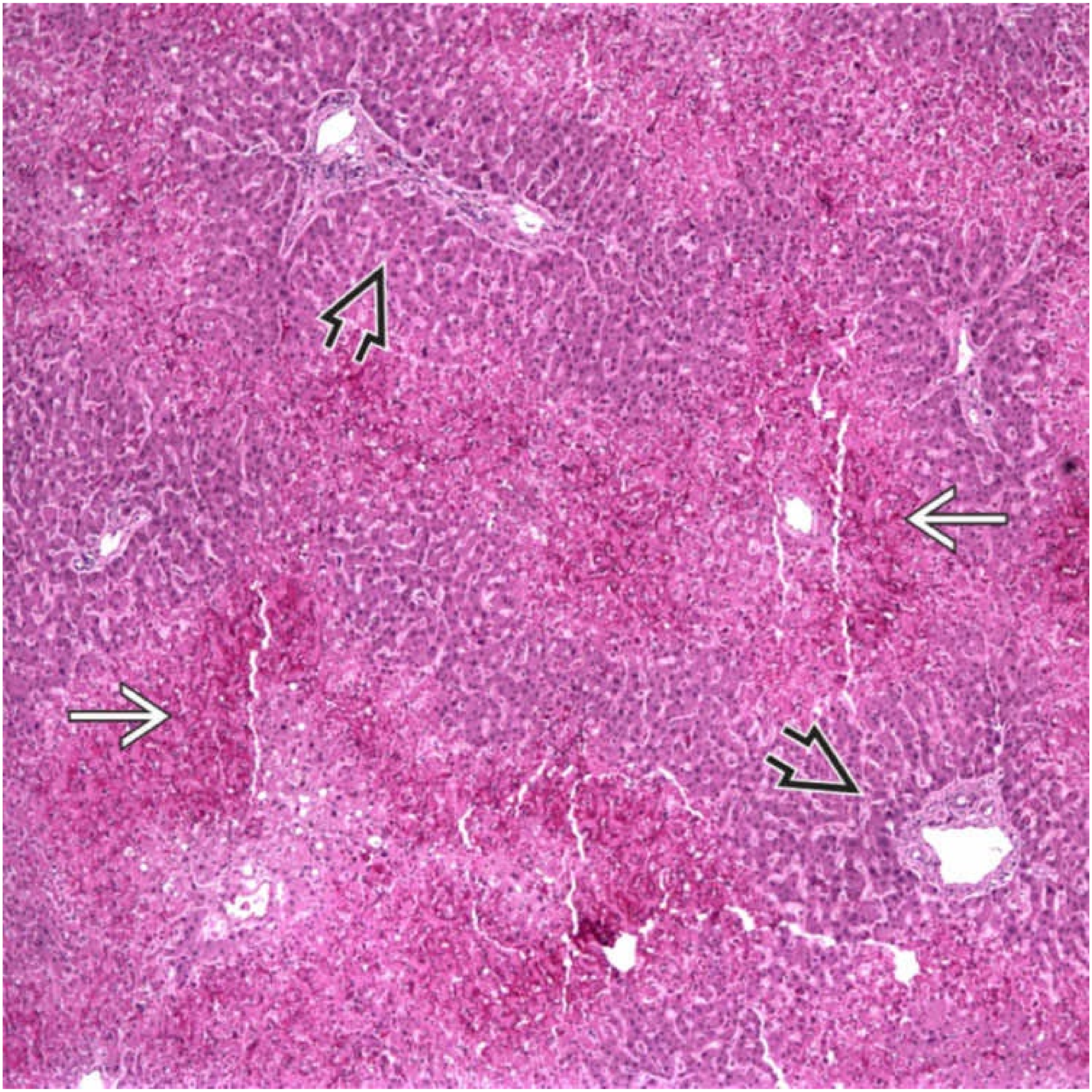
Diagnostic Checklist

- Consider in systemically ill patients or those at risk for thrombosis with rapid, extreme rise in aminotransferases



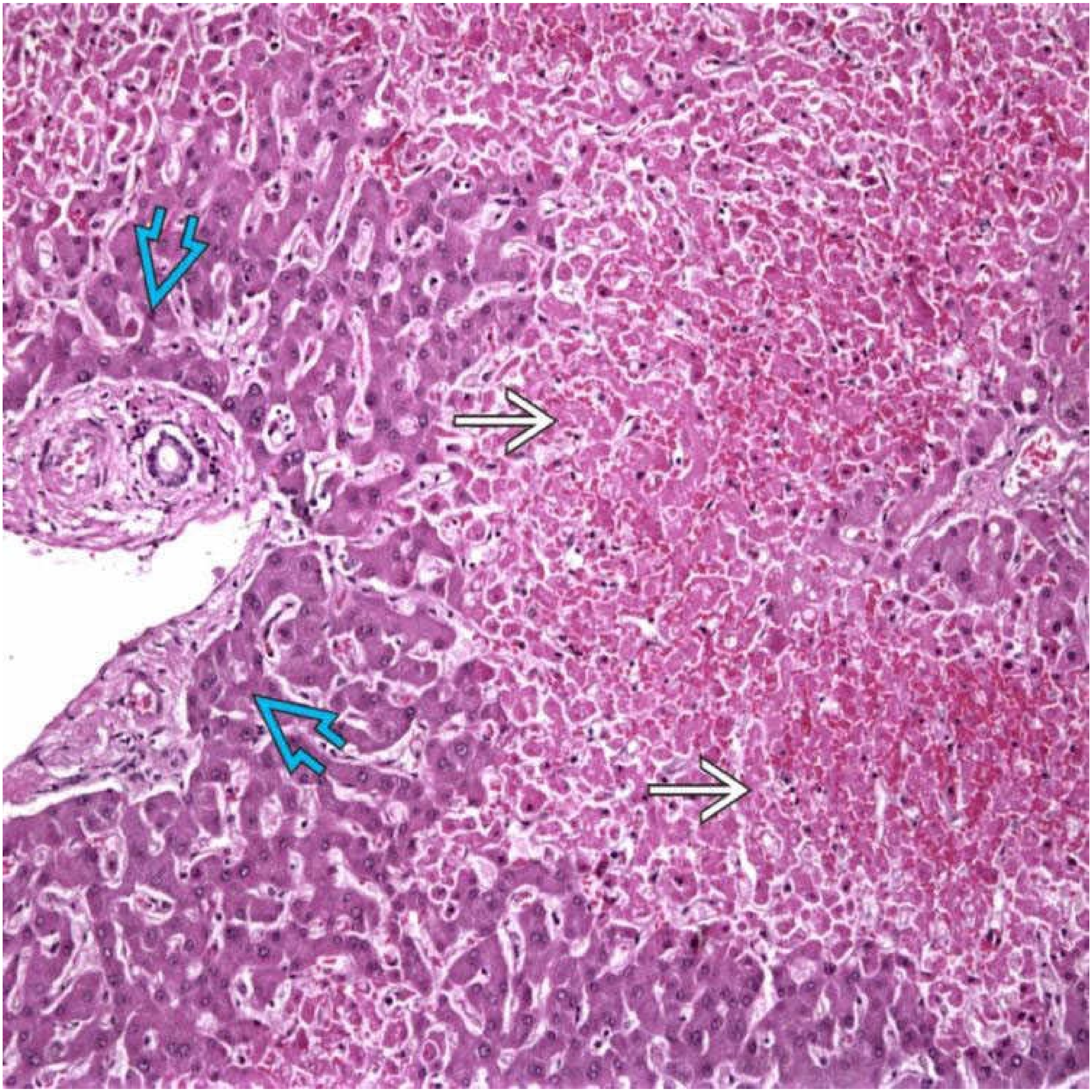
Gross Appearance

This gross photograph illustrates a subcapsular hepatic infarct. The infarcted area shows variegated red hemorrhagic areas ⇨ admixed with necrosis ⇨ .



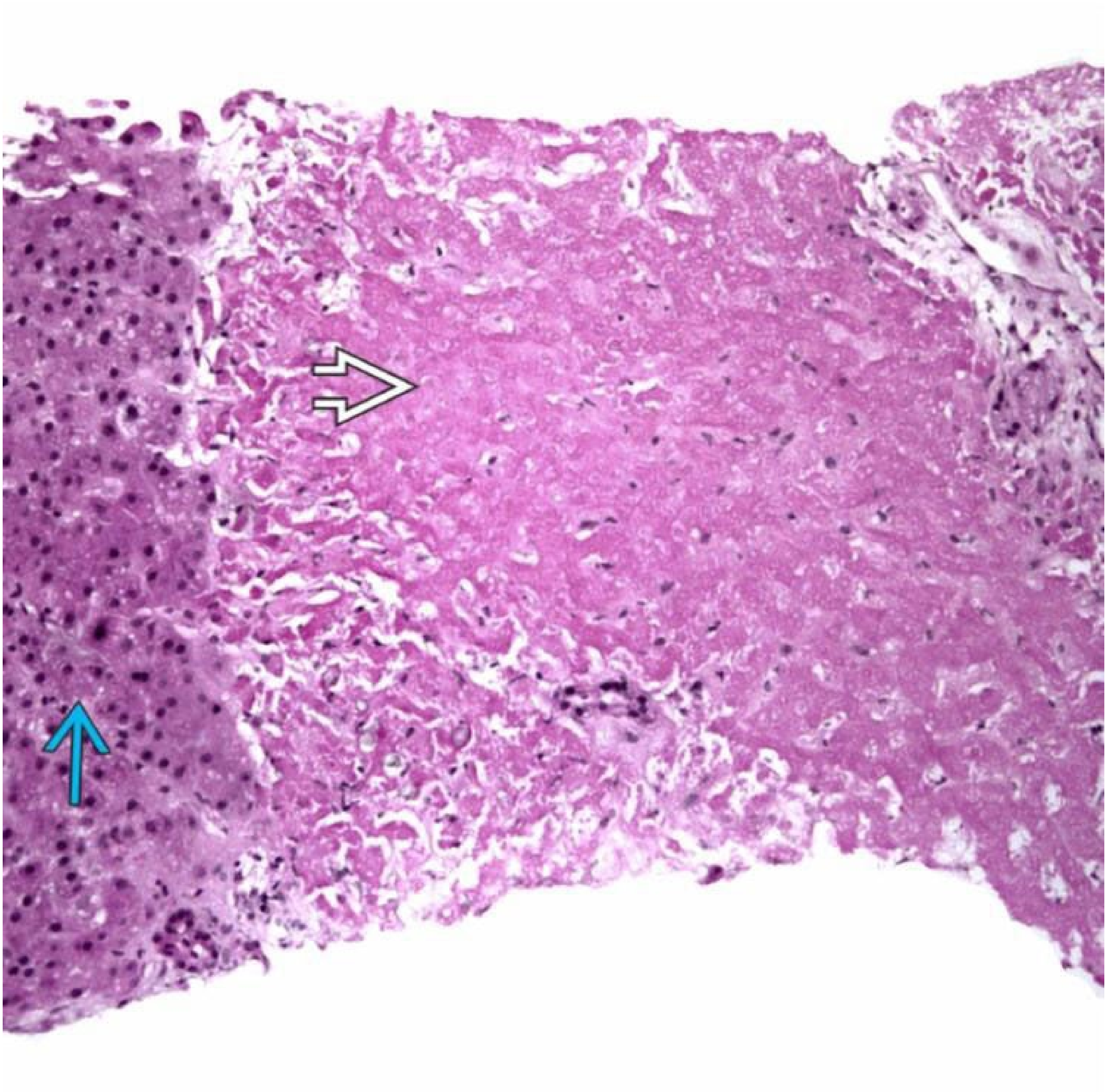
Hepatic Ischemia

This low-power photomicrograph shows zone 3 perivenular hemorrhage and necrosis in a case of hepatic ischemia. The periportal hepatocytes are well preserved .



Zone 3 Necrosis and Hemorrhage

Well-demarcated areas of hepatocyte necrosis and hemorrhage are seen in hepatic ischemia. The hemorrhage corresponds to the red areas seen grossly in "nutmeg" liver. Periportal hepatocytes are well preserved .



Sharply Delineated Necrosis
This liver biopsy demonstrates a sharp distinction between areas of confluent hepatocyte necrosis ⇨ and preserved adjacent hepatocytes → .

TERMINOLOGY

Synonyms

- Ischemic hepatitis or hypoxic hepatitis
- Shock liver
- Hepatic infarction

Definitions

- Liver injury due to reduced blood flow

ETIOLOGY/PATHOGENESIS

Systemic Hypotension &/or Hypoxemia

- Cardiac failure or circulatory shock of any cause

Vascular Obstruction

- Caused by stasis, endothelial injury, and hypercoagulable state
  - 1 or more vessels may be involved
- In transplant patients, anastomotic complications lead to vascular thromboses
- In native livers, usually require obstruction of 2 vessels to result in clinically significant ischemia
  - Greater collateralization present in native livers, but allografts subject to injury with single vessel obstruction

CLINICAL ISSUES

Presentation

- Often asymptomatic
- May exhibit mild jaundice
- Severely affected patients may present with acute liver failure

Laboratory Tests

- Rapid and extreme rise in serum aminotransferases, often identified by screening laboratory tests
  - May be followed by liver failure
  - If patient survives, enzymes then normalize rapidly
- Marked elevation of lactate dehydrogenase (LDH)

Treatment

- Treat underlying cause of ischemia
- Supportive care

Prognosis

- Depends on duration and extent of liver injury
  - In severe cases, often accompanied by multisystem organ failure and poor prognosis
- Most cases are brief and followed by recovery
  - Many cases are likely subclinical
- Hepatic abscess may occur if necrotic tissue is colonized by organisms

MACROSCOPIC

General Features

- Variably present gross abnormalities
  - Infarcts evident as hyperemic areas
  - "Nutmeg" liver
  - Serpiginous, red discoloration representing zones of necrosis and hemorrhage
  - Common autopsy finding

MICROSCOPIC

Histologic Features

- Range of findings, depending on location and extent of ischemic insult
  - Different regions of liver can be variably affected
  - Needle biopsies may not be representative of extent or severity of injury
- Sharply demarcated zones of coagulative hepatocyte necrosis
  - Collapse of liver cell plates seen on reticulin stain
  - Sinusoidal congestion
  - May see cholestasis at periphery of necrotic areas
  - With cardiac failure or shock, zone 3/perivenular hepatocytes most often affected
    - May extend into zone 2
  - Zone 1 necrosis more typical of diseases with intravascular fibrin deposition
    - Disseminated intravascular coagulation, toxemia of pregnancy
- Hepatic infarct: Ischemic necrosis of 2 or more contiguous and complete acini
- Hepatocyte swelling
- Minimal inflammation
- Aggregates of ceroid pigment-laden macrophages in hepatic lobules following resolution
- Dystrophic calcification may eventually develop

DIFFERENTIAL DIAGNOSIS

Infection

- In infection, necrotic areas are nonzonal ("geographic" necrosis)
  - Herpes simplex and adenovirus hepatitis cause nonzonal confluent necrosis
  - Viral inclusions can usually be found on H&E &/or immunohistochemistry

Drug-Induced Liver Injury

- Acetaminophen and cocaine also cause zone 3 hepatocyte necrosis
- Distinction based on history and other clinical findings

Chronic Passive Congestion

- Causes centrilobular hepatocyte atrophy and sinusoidal dilatation
- Usually lacks zonal ischemic necrosis, infarcts
- History and laboratory values may be helpful

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Consider in systemically ill patients or those at risk for thrombosis with rapid, extreme rise in aminotransferases

SELECTED REFERENCES

1. Ford, RM, et al. Liver disease related to the heart. *Transplant Rev (Orlando)*. 2015; 29(1):33–37.
2. Henrion, J. Hypoxic hepatitis. *Liver Int*. 2012; 32(7):1039–1052.
3. Ebert, EC. Hypoxic liver injury. *Mayo Clin Proc*. 2006; 81(9):1232–1236.
4. Denis, C, et al. Acute hypoxic hepatitis (‘liver shock’): still a frequently overlooked cardiological diagnosis. *Eur J Heart Fail*. 2004; 6(5):561–565.
5. Giallourakis, CC, et al. The liver in heart failure. *Clin Liver Dis*. 2002; 6(4):947–967. [viii-ix].
6. Seeto, RK, et al. Ischemic hepatitis: clinical presentation and pathogenesis. *Am J Med*. 2000; 109(2):109–113.

Nodular Regenerative Hyperplasia

KEY FACTS

Etiology/Pathogenesis

- Nodular regenerative hyperplasia (NRH) results from changes in hepatic blood flow resulting from obliteration of small portal vein radicles

Clinical Issues

- Symptomatic NRH clinically manifests as portal hypertension and its sequelae

Macroscopic

- Most nodules are 1-3 mm but can be larger

Microscopic

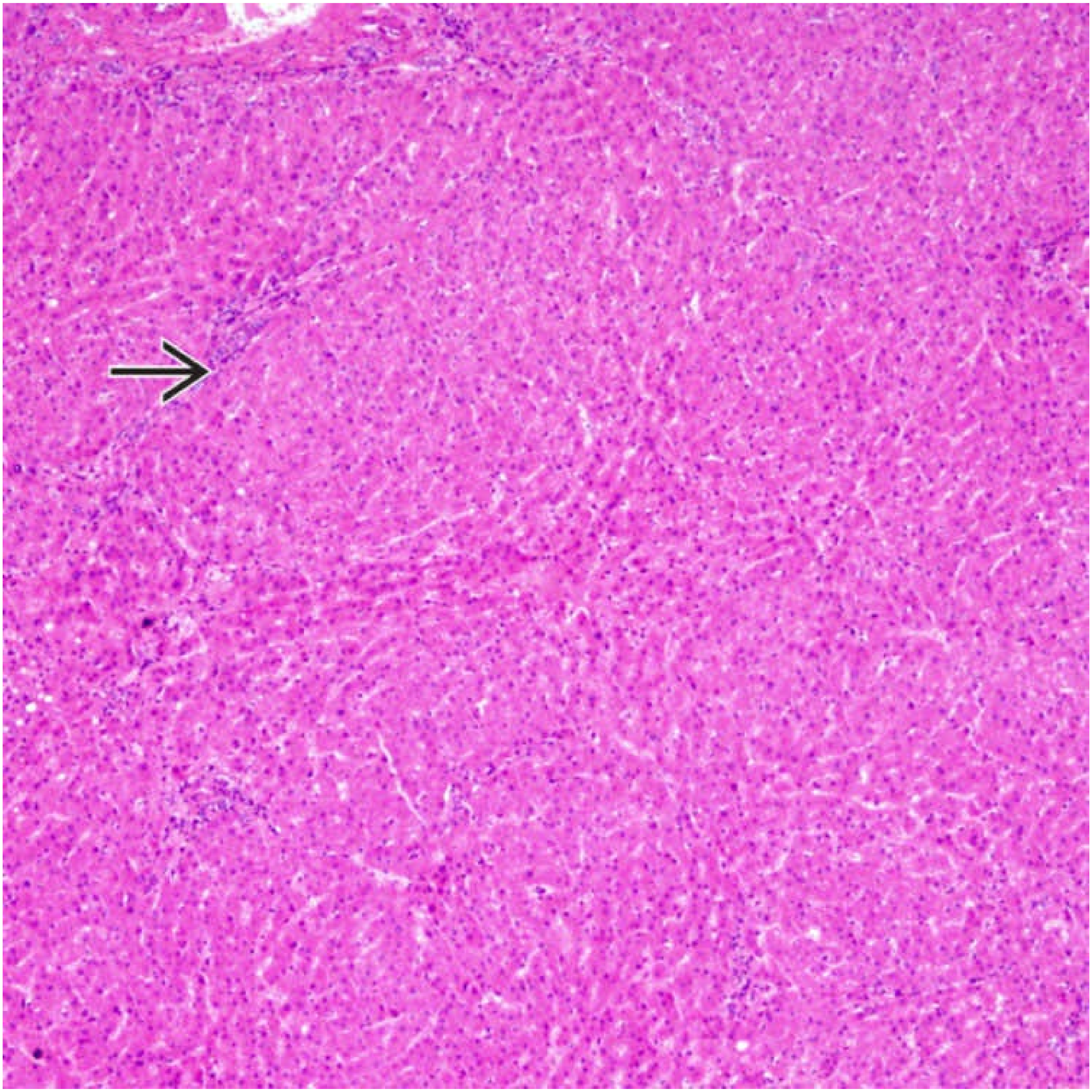
- Diffuse replacement of liver parenchyma by small nodules without fibrous septa
  - Nodules are often vague and ill-defined
  - Typically 1-3 mm
- No fibrous septa between nodules
  - But focal sinusoidal or periportal fibrosis can be seen
- Inflammation is absent
  - Bile ducts and hepatic arterioles are normal

Top Differential Diagnoses

- Cirrhosis
- Focal nodular hyperplasia
- Adenomatosis
- Partial nodular transformation

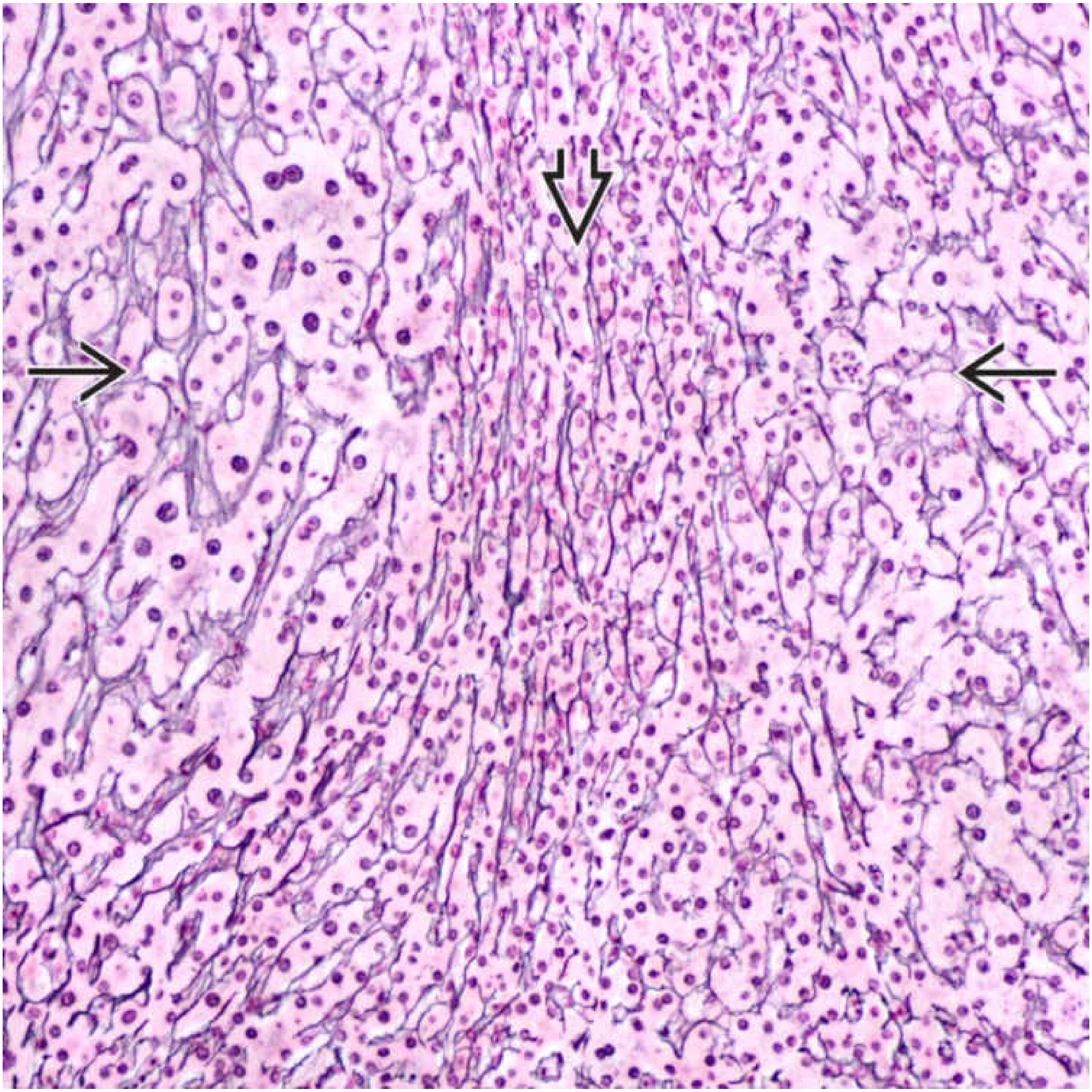
Diagnostic Checklist

• Reticulin stain should be obtained in all cases of unexplained portal hypertension



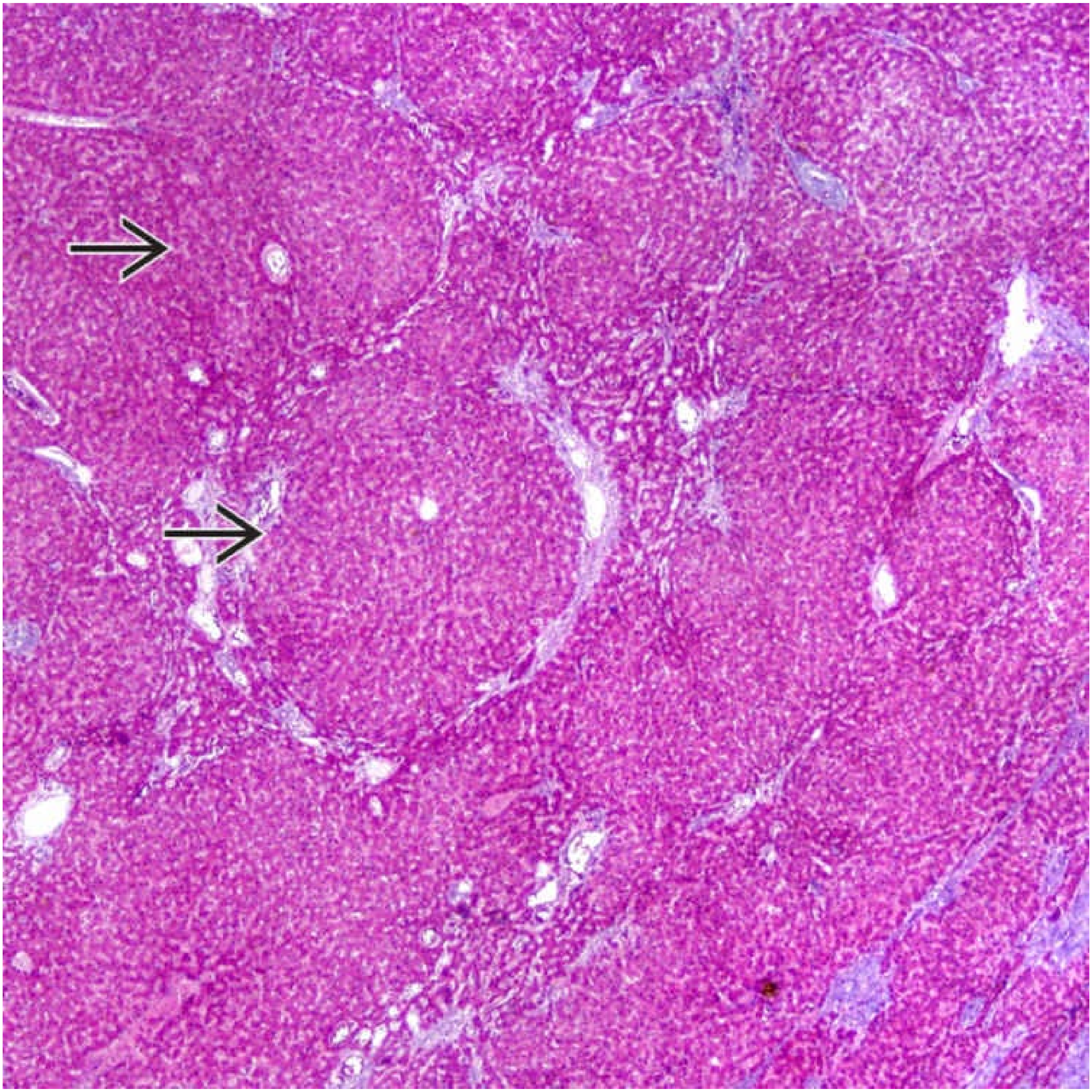
Ill-Defined Nodules

Nodular regenerative hyperplasia (NRH) is characterized by diffuse replacement of liver by small nodules →. Nodules are typically 1-3 mm in size but can be as large as 1 cm.



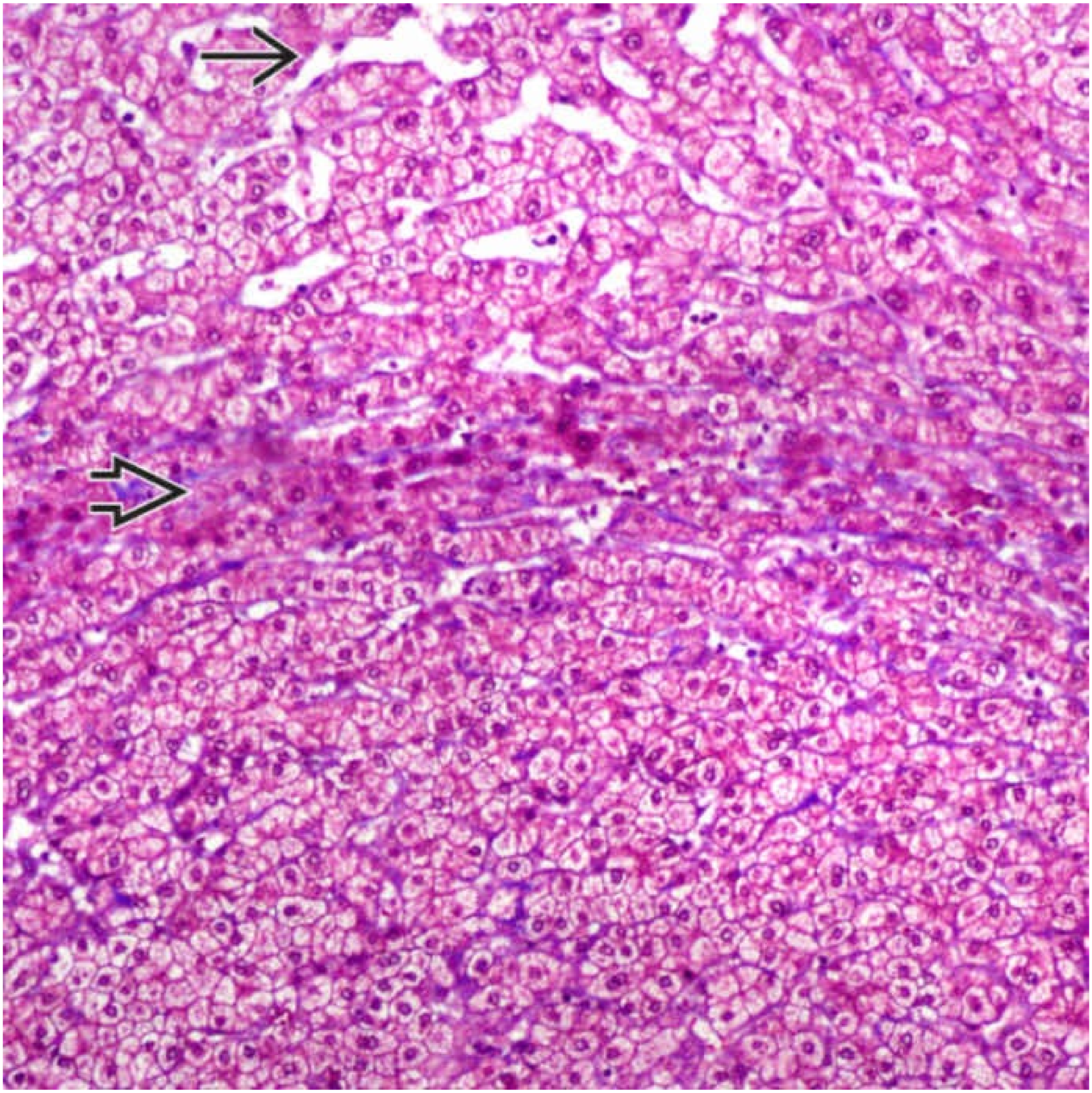
Reticulin Stain

Reticulin stain highlights the nodules →. The reticulin network is compressed in the parenchyma between the nodules ⇨. Reticulin stain is very useful for the diagnosis as the nodularity in NRH can be subtle.



Trichrome Stain

Trichrome stain highlights the nodules →. By definition, there are no fibrous septa between the nodules in nodular regenerative hyperplasia.



No Fibrous Septa
Trichrome stain shows absence of fibrous septa at the periphery of the nodules. This distinguished NRH from cirrhosis. Focal sinusoidal dilatation can be seen in NRH →. The hepatocytes between the nodules are compressed and atrophic ⇨ .

TERMINOLOGY

Abbreviations

- Nodular regenerative hyperplasia (NRH)

Definitions

- Pattern of liver injury, associated with many underlying causes, that does not represent specific entity
  - Formation of nodules with minimal or no fibrosis
  - Believed to be related to ischemic atrophy with secondary nodular hyperplasia in areas with good

blood flow

ETIOLOGY/PATHOGENESIS

Mechanism

- Results from changes in hepatic blood flow resulting from obliteration of small portal vein radicles
- Obliterative changes in some portal vein radicles lead to localized areas of decreased blood flow and atrophy
- Portal hypertension results from obliterative portal venopathy or sinusoidal compression by nodules

CLINICAL ISSUES

Presentation

- More prevalent in elderly population but can occur in children
- Underlying disease is often clinically evident long before NRH becomes symptomatic
- Symptomatic NRH manifests as portal hypertension and its sequelae: Variceal bleeding, ascites, and splenomegaly
- NRH should always be considered in the setting of portal hypertension without cirrhosis

Laboratory Tests

- Liver transaminases and serum bilirubin levels usually normal; alkaline phosphatase elevated in 25% of cases

Treatment

- Identification and treatment of underlying etiology
- Portosystemic shunt for portal hypertension

IMAGING

Radiographic Findings

- Imaging can be normal or show diffuse nodularity mimicking cirrhosis

MACROSCOPIC

General Features

- Diffuse replacement of liver parenchyma by small nodules
    - Most nodules are 1-3 mm but can be larger

MICROSCOPIC

Histologic Features

- Diagnosis may be difficult in small biopsies
  - Vague, ill-defined, diffuse parenchymal nodules
  - ○ Hepatocytes in nodule arranged in plates that are 1-2 cells thick
  - ○ Hepatocytes between nodules are small and atrophic; often compressed into thin, parallel plates
  - – Variation in hepatocytes within and between nodules is best demonstrated on reticulin stain

○ Regenerative features (large nuclei, binucleation) may be seen

- Sinusoidal dilation in areas of hepatocellular atrophy
- There are no fibrous septa between the nodules, but focal sinusoidal or periportal fibrosis can be seen
- Occlusion of small portal vein radicals occlusion can occur; larger portal veins are generally normal
- Inflammation is absent; bile ducts and hepatic arterioles are normal

DIFFERENTIAL DIAGNOSIS

Cirrhosis

- Fibrous septa around nodules distinguishes cirrhosis from NRH

Focal Nodular Hyperplasia

- Usually solitary, < 5 cm
- Central scar and fibrous septa with aberrant arterioles and ductular reaction

Adenomatosis

- Varying sized nodules, typically larger than nodules in NRH (several cm)
- Multiple lesions but generally do not involve liver diffusely and uniformly

Partial Nodular Transformation

- Single or multiple nodules at or close to hepatic hilum
- Size of nodules larger than nodules in NRH (3-5 cm)

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Reticulin stain should be obtained in all cases of unexplained portal hypertension

SELECTED REFERENCES

1. Wang, HM, et al. Nodular regenerative hyperplasia of the liver. *J Chin Med Assoc*. 2008;

71(10):523–527.
2.Reshamwala, PA, et al. Nodular regenerative hyperplasia: not all nodules are created equal. *Hepatology*. 2006; 44(1):7–14.
3.Shimamatsu, K, et al. Role of ischemia in causing apoptosis, atrophy, and nodular hyperplasia in human liver. *Hepatology*. 1997; 26(2):343–350.
4.Wanless, IR. Micronodular transformation (nodular regenerative hyperplasia) of the liver: a report of 64 cases among 2,500 autopsies and a new classification of benign hepatocellular nodules. *Hepatology*. 1990; 11(5):787–797.

SECTION 8
TRANSPLANTATION PATHOLOGY

OUTLINE

Preservation Injury

KEY FACTS

Terminology

- Tissue damage sustained during graft harvesting, preservation, transportation, and reperfusion

Etiology/Pathogenesis

- Cold ischemia
  - Prolonged storage in preservation solutions
- Warm ischemia
  - Compromised blood flow to liver at body temperature before and during harvesting
  - Resumption of blood flow after implantation

Clinical Issues

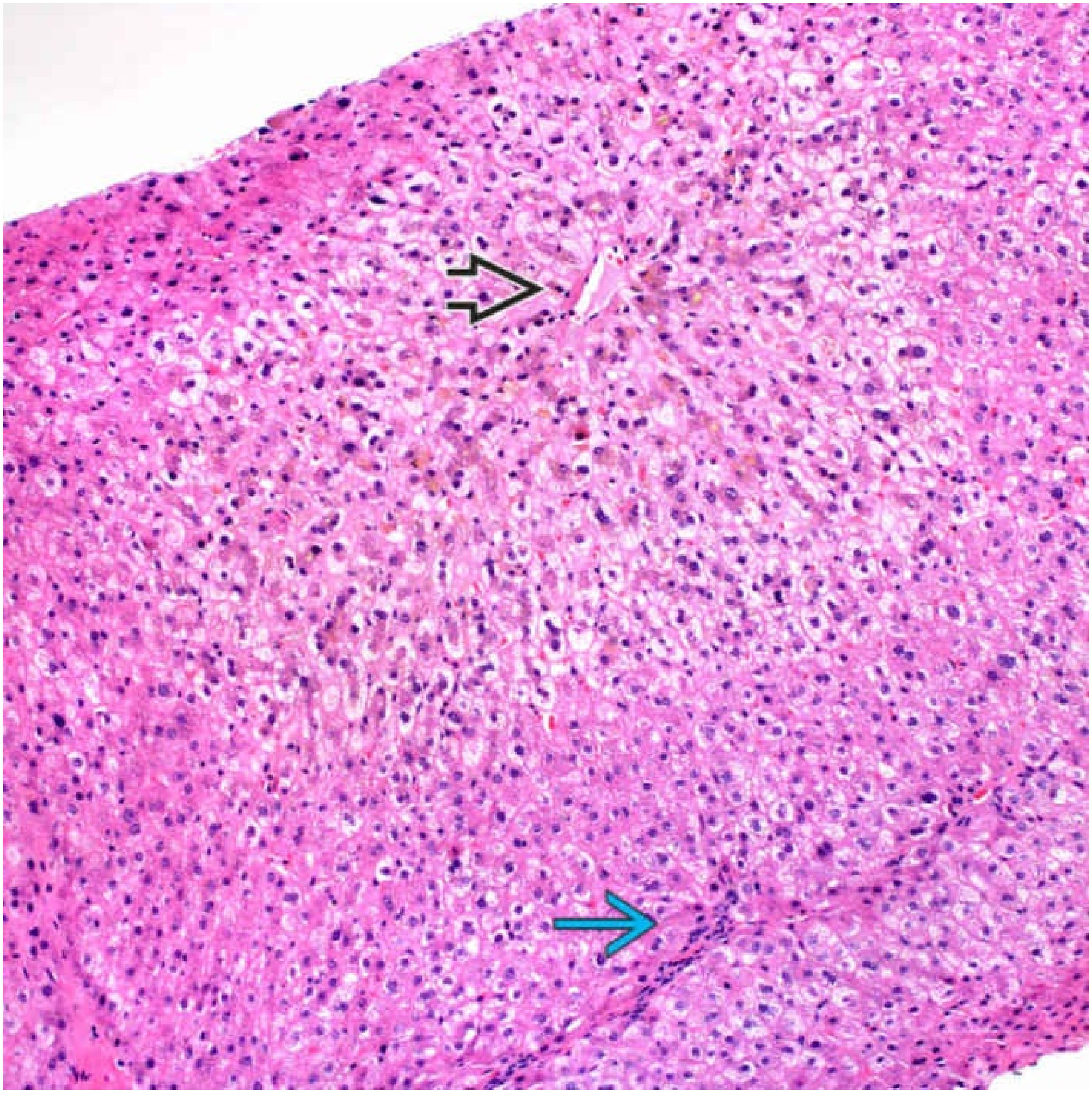
- Elevation of serum transaminases and poor bile production within first 24-48 hours after revascularization
- Enzyme levels typically decrease progressively within several days if graft survives injury
- Complete resolution in most cases
- Graft failure in rare cases (primary nonfunction)

Microscopic

- Hepatocyte ballooning and microvesicular/small droplet steatosis, imparting distinctive pale appearance on low-power view
- Hepatocyte detachment from each other, scattered acidophil bodies, and spotty necrosis
- Confluent necrosis in severe cases, can also involve periportal areas
- Cytoplasmic and canalicular cholestasis, more pronounced at zone 3
- Varying degree of neutrophilic infiltrates in lobules
- No significant portal inflammation in general

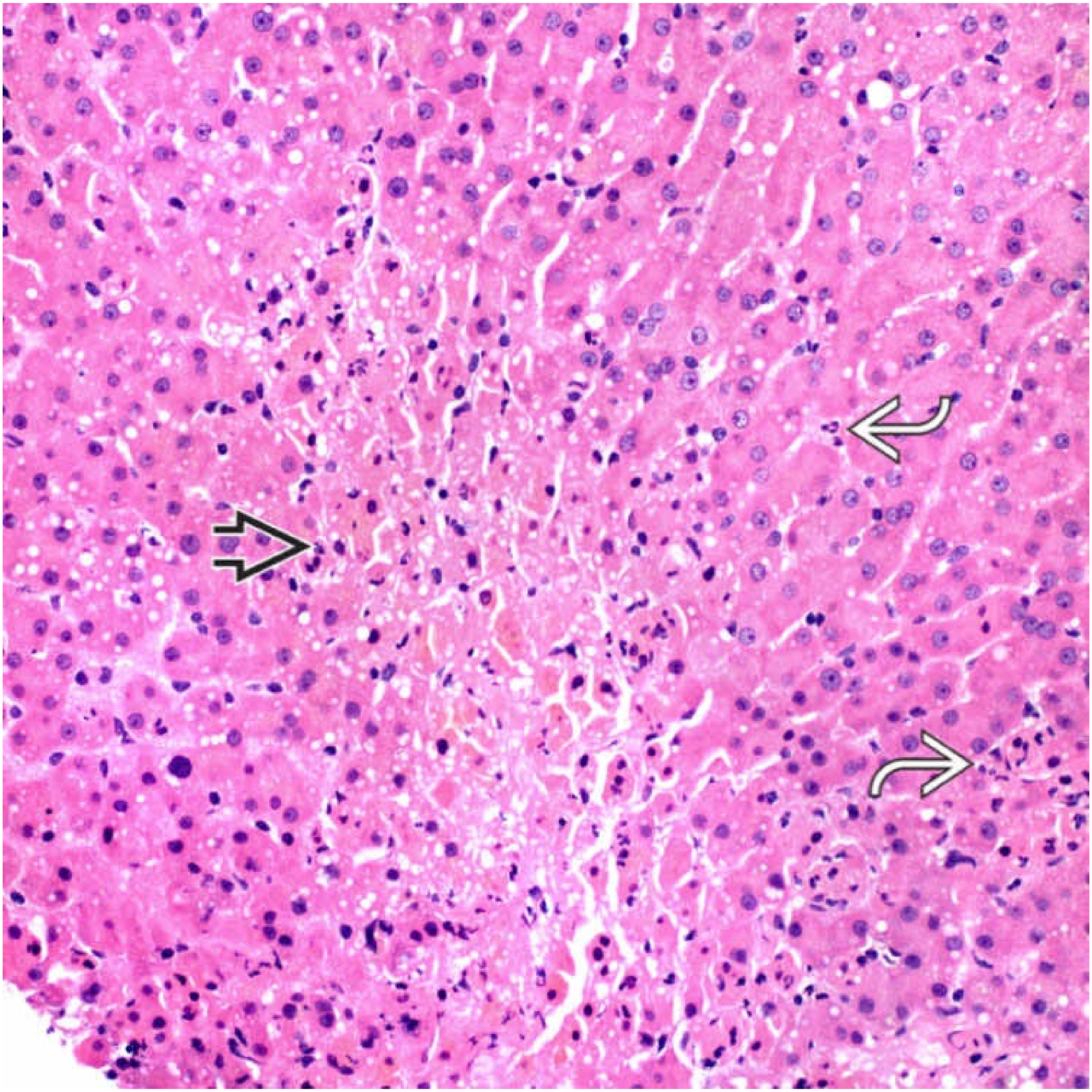
Top Differential Diagnoses

- Antibody-mediated rejection
- Hepatic artery thrombosis
- Hepatic vein stenosis and thrombosis
- Biliary obstruction



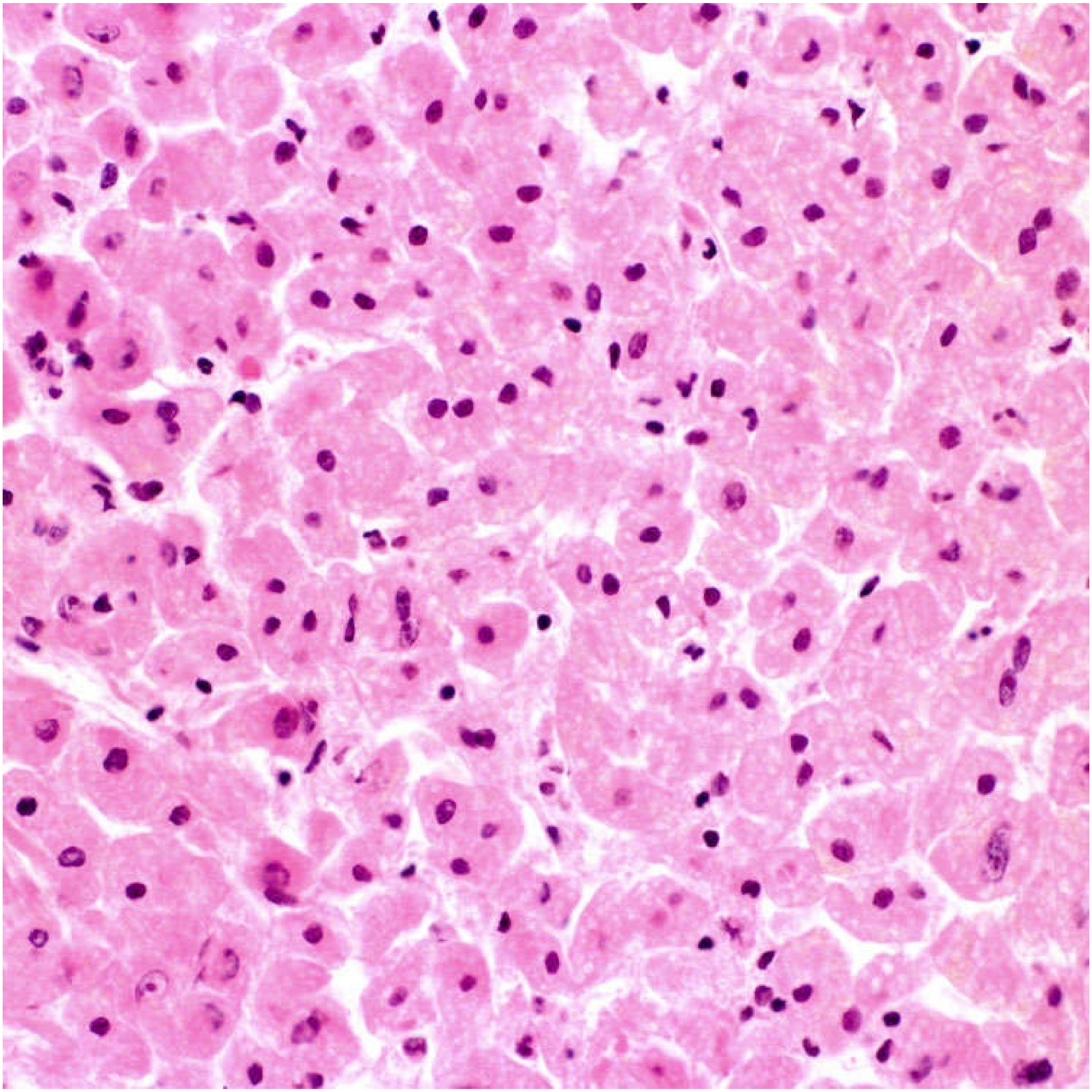
Zone 3 Hepatocyte Ballooning

Mild preservation injury features hepatocyte ballooning around the terminal hepatic venule, imparting a distinctive pale appearance at zone 3 on low power. Note the presence of a small unremarkable portal tract.



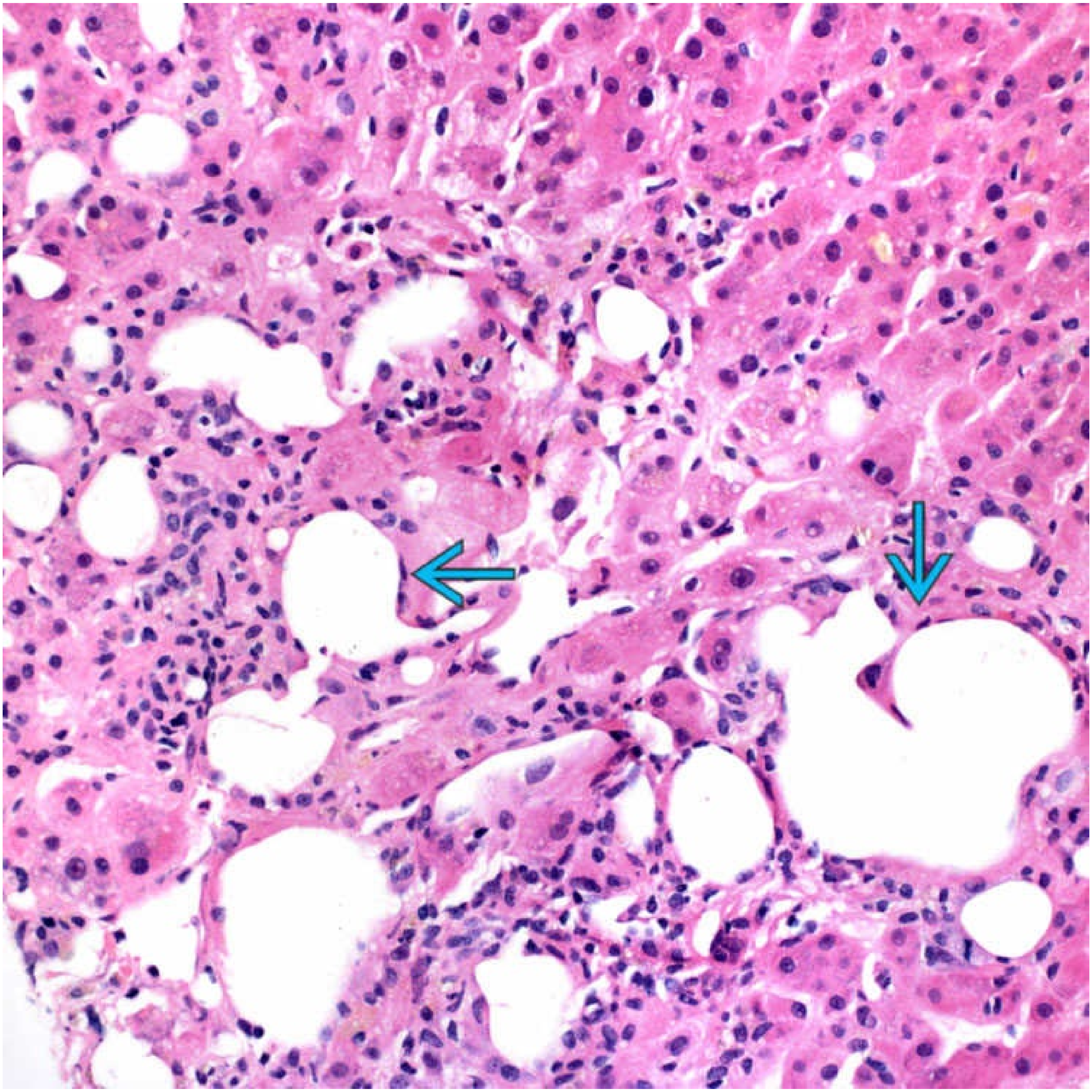
Zone 3 Necrosis

This case shows typical features of preservation injury demonstrated in a postreperfusion allograft biopsy. There is zone 3 necrosis and microvesicular steatosis, along with scattered neutrophils in the lobules.



Coagulative Necrosis

This posttransplant day 1 biopsy shows severe preservation injury, featuring extensive coagulative necrosis with dyscohesive hepatocytes. Clinically, the allograft showed primary nonfunction that required retransplantation.



Lipopeliosis

This allograft biopsy performed 6 days after transplantation shows large fat droplets in extracellular spaces →, which are released from damaged steatotic hepatocytes secondary to preservation injury (lipopeliosis). Note the presence of inflammatory cells around the fat droplets.

TERMINOLOGY

Synonyms

- Preservation/reperfusion injury
- Harvesting injury
- Ischemia and reperfusion injury

Definitions

- Tissue damage sustained during graft harvesting, preservation, transportation, and reperfusion
- 1 of major causes of initial graft dysfunction

ETIOLOGY/PATHOGENESIS

Ischemic Injury

- Occurs in 4 stages
  - Prepreservation injury
  - Cold preservation
  - Rewarming
  - Reperfusion injury
- 2 types of ischemic injury
  - Cold ischemia
    - Prolonged storage in preservation solutions (should be < 12 hours)
    - Preferentially targets sinusoidal endothelial cells
  - Warm ischemia
    - Compromised blood flow to liver at body temperature before and during harvesting
    - Resumption of blood flow after implantation
    - Primarily damages hepatocytes
- Bile duct epithelium, Kupffer cells, and Ito cells sensitive to both cold and warm ischemia
- Severity of injury depends on type and duration of ischemic stress
- Preexisting donor risk factors
  - Severe large droplet macrovesicular steatosis (> 30%)
  - Donation after cardiac death
  - Prolonged stay in intensive care unit
  - Increasing donor age

CLINICAL ISSUES

Presentation

- Elevation of serum transaminases and poor bile production within first 24-48 hours after revascularization
  - Enzyme levels typically decrease progressively within several days if graft survives injury
- Clinical resolution usually observed within 1-4 weeks
  - Abnormal liver tests may persist for several months if injury is severe

Treatment

- No specific therapy

Prognosis

- Complete resolution in most cases
  - Graft failure in rare cases (primary nonfunction)
- Higher incidence of subsequent acute and chronic rejection
- Higher incidence of biliary complications, such as ischemic cholangiopathy

MICROSCOPIC

Histologic Features

- Hepatocyte injury, primarily zone 3
  - Hepatocyte ballooning and microvesicular/small droplet steatosis, imparting distinctive pale appearance on low power
  - Dyscohesive hepatocytes, scattered acidophil bodies, and spoty necrosis
  - Confluent necrosis in severe cases, can also involve periportal areas
  - Damaged hepatocytes may release preexisting fat into extracellular spaces (lipopeliosis)
- Varying degree of neutrophilic infiltrates in lobules
  - No significant portal inflammation in general
- Biliary/cholestatic changes
  - Cytoplasmic and canalicular cholestasis, more pronounced in zone 3
  - Bile duct degeneration and detachment of duct epithelium from basement membrane
  - Ductular reaction, sometimes with ductular cholestasis and bile plugs
  - No significant bile duct injury in most cases
- Resolving preservation injury with regenerative changes of hepatocytes
  - Increased mitotic activity, nuclear enlargement, thickened cell plates, and frequent binucleation
  - Mild ballooning and cytoplasmic cholestasis may persist for several weeks
  - Zone 3 histiocytes and other inflammatory cells

DIFFERENTIAL DIAGNOSIS

Antibody-Mediated Rejection

- Preformed donor-reactive antibodies in recipient
- Hemorrhagic necrosis of graft with fibrin thrombi
- Fibrinoid necrosis of hepatic artery branches

Hepatic Artery Thrombosis

- Doppler ultrasound and angiography are diagnostic
- Massive or zone 3 coagulative necrosis
- Bile duct necrosis

Hepatic Vein Stenosis and Thrombosis

- Doppler ultrasound and venography are diagnostic
- Resembles Budd-Chiari syndrome clinically

• Zone 3 congestion, hemorrhage, and necrosis

Biliary Obstruction

• Cholangiography is diagnostic
• Portal edema, prominent ductular reaction, and portal neutrophilic infiltrates

“Surgical Hepatitis”

• Clusters of neutrophils in sinusoids, without necrosis

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

• Zone 3 hepatocyte damage characterized by ballooning, necrosis, and cholestasis

SELECTED REFERENCES

1. Ali, JM, et al. Analysis of ischemia/reperfusion injury in time-zero biopsies predicts liver allograft outcomes. *Liver Transpl*. 2015; 21(4):487–499.
2. Westerkamp, AC, et al. Similar outcome after transplantation of moderate macrovesicular steatotic and nonsteatotic livers when the cold ischemia time is kept very short. *Transpl Int*. 2015; 28(3):319–329.

Antibody-Mediated Rejection

KEY FACTS

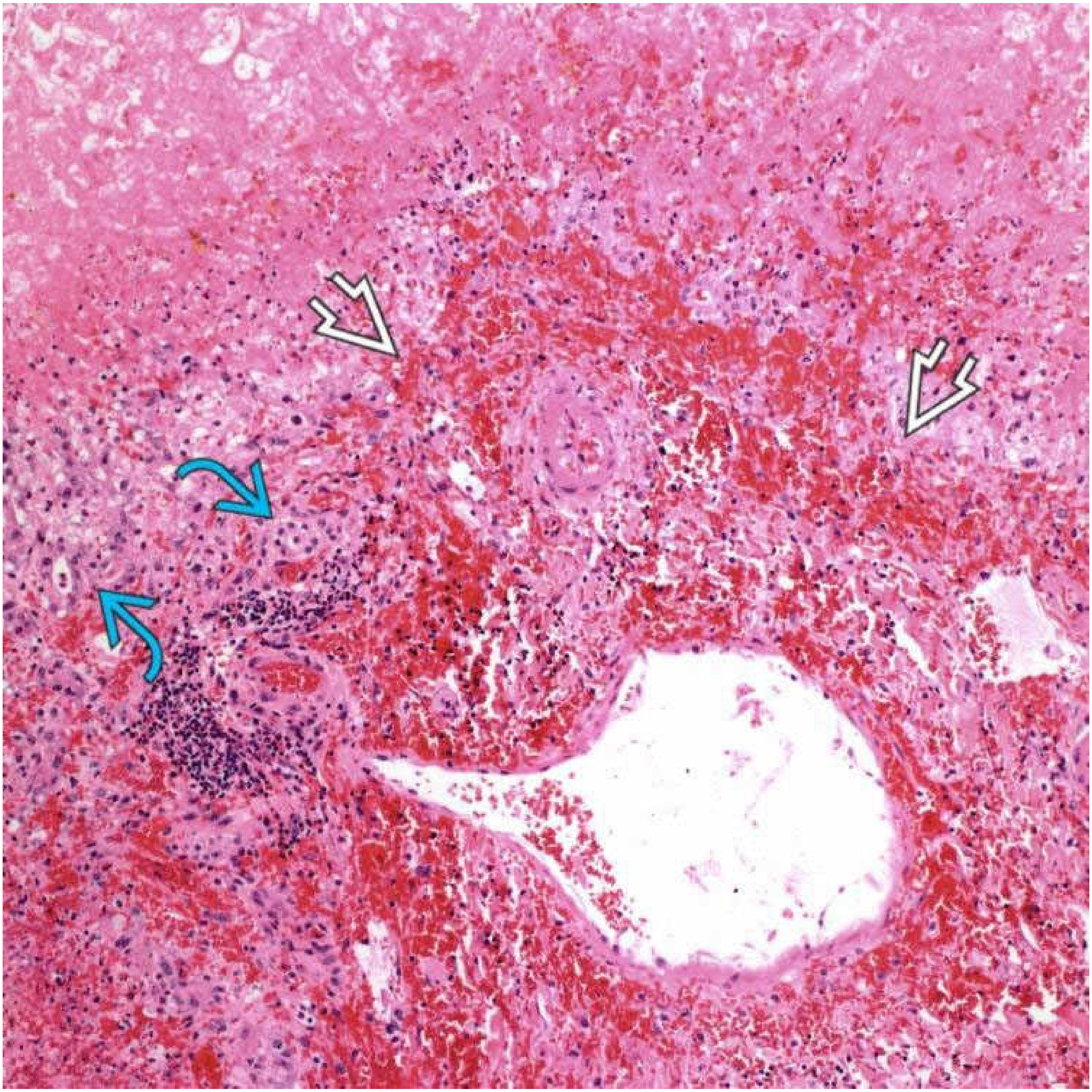
Terminology

- Graft dysfunction mediated by antibodies directed against donor antigens
  - Preformed antibodies
  - Donor-specific antibodies (DSA) developed after transplantation

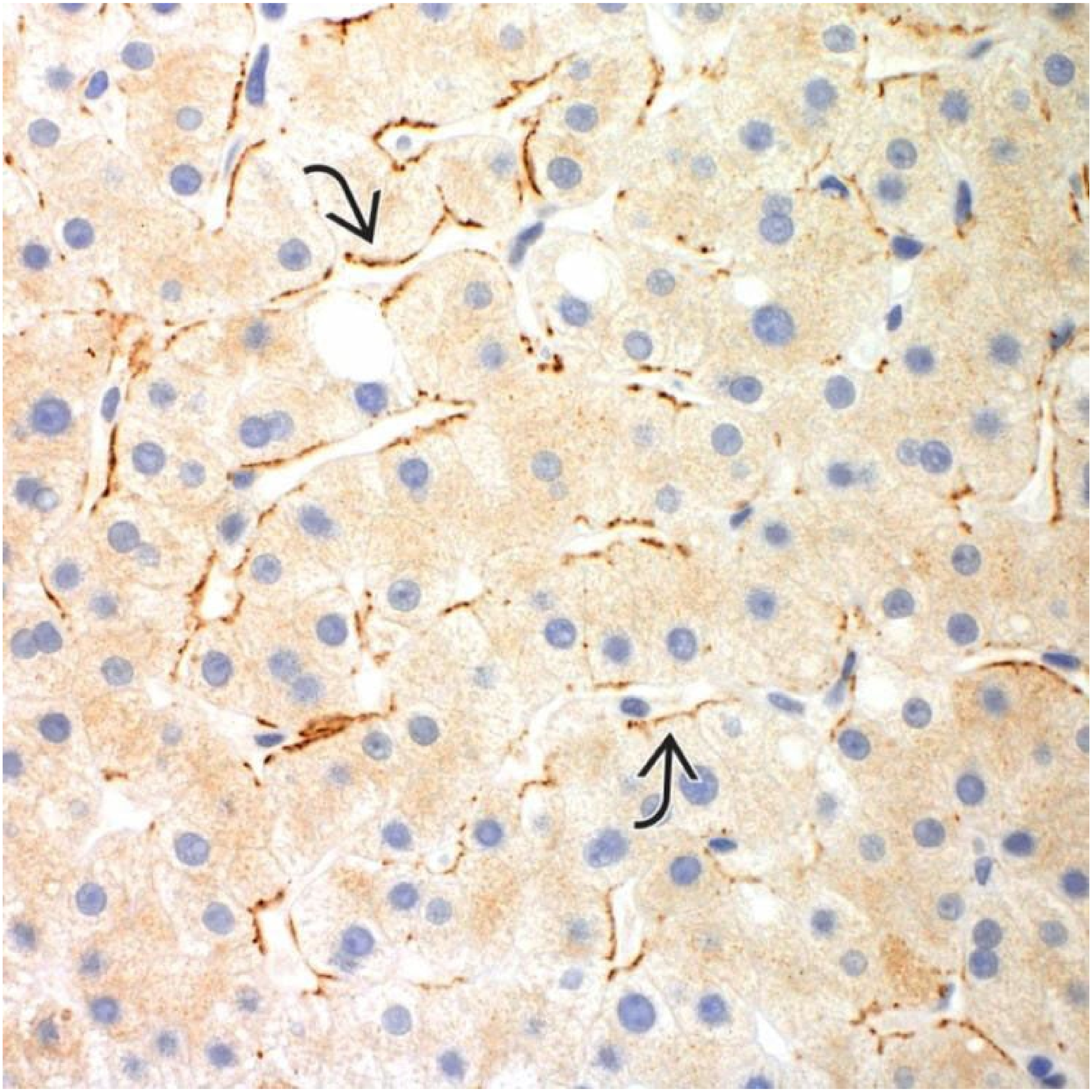
Microscopic

- Hyperacute antibody-mediated rejection (AMR)
  - Fibrin thrombi in portal and central veins and sinusoids
  - Neutrophilic &/or fibrinoid arteritis
  - Patchy or massive hemorrhagic hepatocyte necrosis
- Acute AMR (Banff criteria 2016)
  - Definite (all following 4 criteria required)
    - Histologic pattern of injury
    - Positive serum DSA
    - Diffuse (> 50%) C4d deposition
    - Reasonable exclusion of other insults that might cause similar injury
  - Suspicious (both following criteria required)
    - Positive serum DSA
    - C4d core + H-score = 3 or 4
  - Indeterminate (requires following first 2 + 3 or 4)
    - C4d-score + H-score ≥ 2
    - DSA is not available, equivocal, or negative
    - C4d is not available, equivocal, negative
    - Coexisting insult might be contributing to similar injury
- Chronic AMR (Banff criteria 2016)
  - Probable (all following 4 criteria required)
    - Histologic pattern of injury
    - Recent (< 3 months) positive serum DSA
    - At least focal (> 10%) C4d deposition in portal microvasculature
    - Reasonable exclusion of other insults that might cause similar injury

○ Possible
  – As above, but C4d is minimal (< 10%) or absent

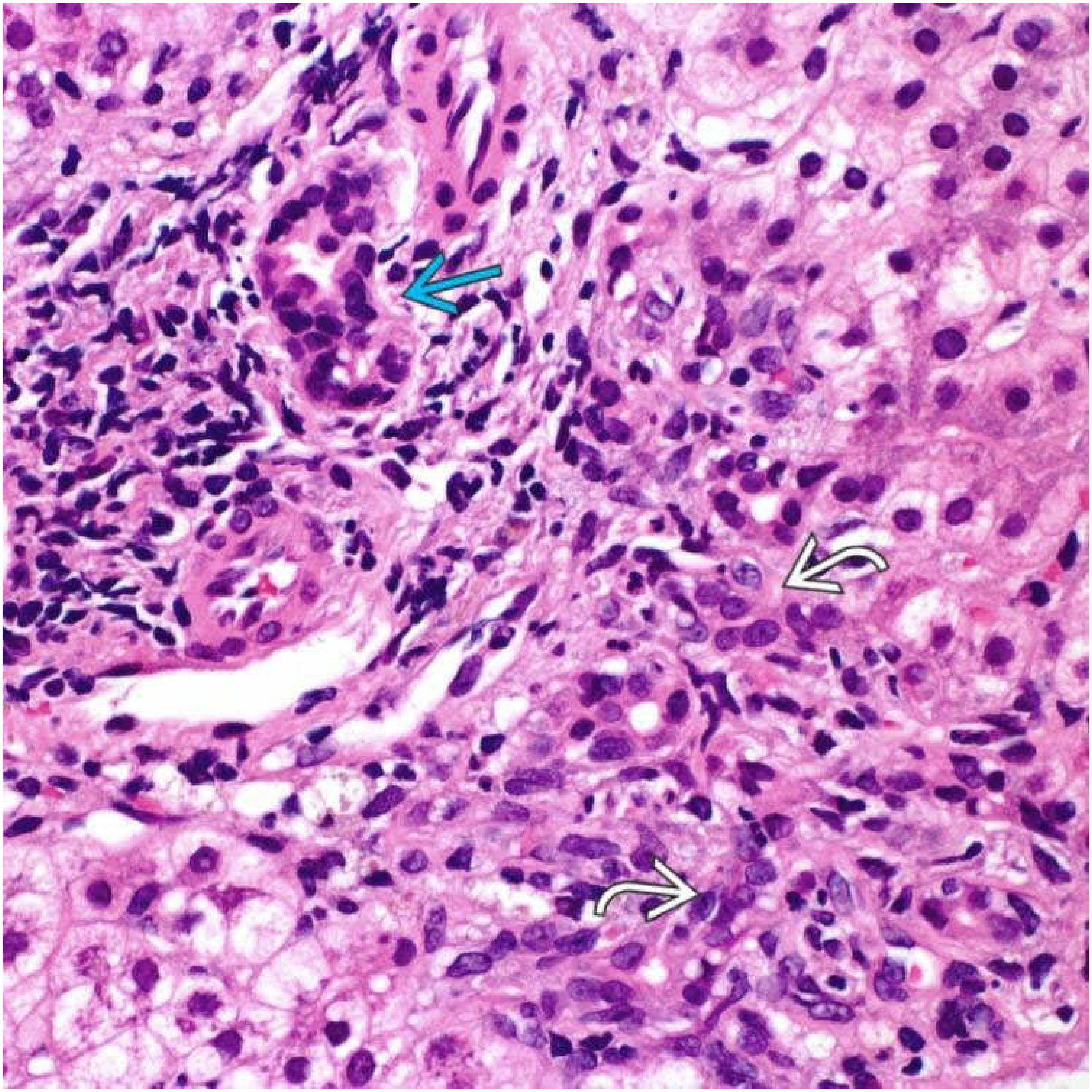


Hyperacute Antibody-Mediated Rejection
This case of hyperacute AMR features massive, panacinar hemorrhagic necrosis. Hemorrhage into portal tracts is evident. Note the lack of significant inflammatory cell infiltrates. Bile duct damage is also seen.



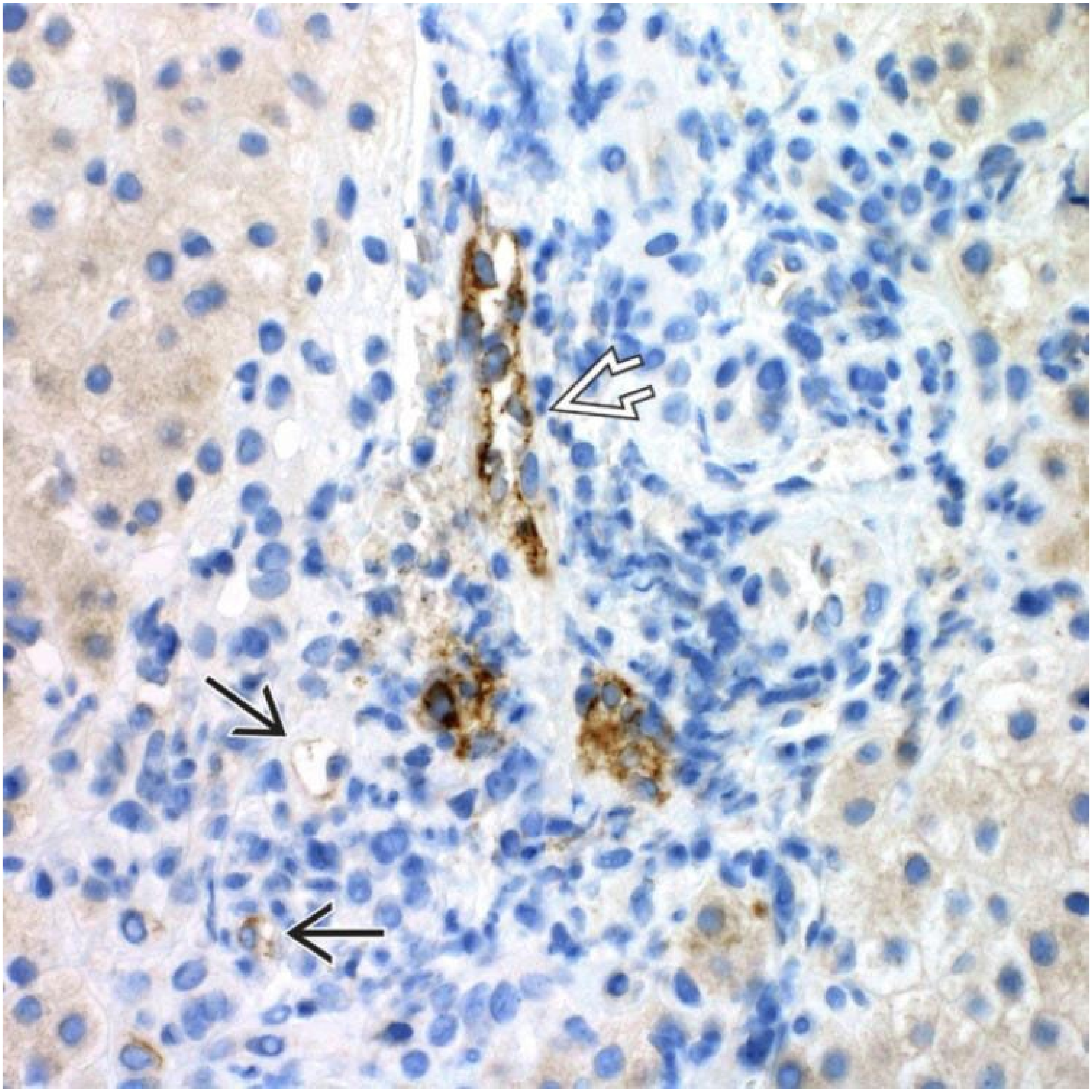
C4d Immunostaining

This patient was diagnosed with late-onset acute rejection 10 days prior and was treated for T cell-mediated rejection. His liver enzymes remained elevated, however. This follow-up biopsy shows features of resolving rejection and patchy sinusoidal C4d immunoreactivity suggesting a role for AMR.



Acute Antibody-Mediated Rejection

An allograft biopsy performed 36 days after transplantation shows features suggestive of biliary obstruction with ductular reaction . Bile duct injury is also noted . No evidence of biliary obstruction is demonstrated by image studies, however.



C4d Immunostaining
Continuous linear C4d immunoreactivity is observed in endothelial cells lining the portal veins ➩ and capillaries → in nearly every portal tract present in this biopsy. The patient is also DSA(+), confirming the diagnosis of acute AMR.

TERMINOLOGY

Abbreviations

- Antibody-mediated rejection (AMR)
- Donor-specific antibodies (DSA)

Synonyms

- Humoral rejection

Definitions

- Graft dysfunction mediated by antibodies directed against donor antigens

ETIOLOGY/PATHOGENESIS

Preformed Antibodies

- Major ABO blood group isoagglutinins
- Lymphocytotoxic antibodies against MHC antigens

De Novo DSA Development After Transplantation

- Seen in 8-15% of liver transplant recipients

CLINICAL ISSUES

Epidemiology

- Incidence
  - AMR mediated by preformed antibodies
    - Up to 35% in ABO-incompatible transplants
    - < 1% in ABO-compatible transplants
  - AMR mediated by DSA developed after transplantation
    - Unknown

Presentation

- Hyperacute AMR
  - Severe graft dysfunction over period of hours to days following initial short period of normal reperfusion and bile production
  - Seen in ABO-incompatible transplants
- Acute AMR
  - Varying degrees of graft dysfunction in 1st several weeks after transplantation
  - Late onset (> 6 months) can occur
  - Seen in ABO-compatible transplants
  - Also seen in ABO-incompatible transplants treated with B-cell directed immunosuppression
- Chronic AMR
  - Poorly defined

Treatment

- Immunosuppression

- Anti-CD20 antibody (rituximab) therapy
- Plasmapheresis
- Retransplantation

Prognosis

- Graft failure
- Increased incidence of graft complications, such as ischemic cholangiopathy and hepatic artery stenosis

IMAGING

Hepatic Artery Angiogram

- Segmental or diffuse luminal narrowing with poor peripheral filling, indicative of vasospasm

MACROSCOPIC

General Features

- Hyperacute AMR

MICROSCOPIC

Histologic Features

- Hyperacute AMR
  - Fibrin thrombi in portal and central veins and sinusoids
  - Neutrophilic &/or fibrinoid arteritis
  - Patchy or massive hemorrhagic hepatocyte necrosis
  - Portal edema, hemorrhage, ductular reaction, and cholangitis
- Acute AMR (Banff criteria 2016)
  - Definite (all following 4 criteria required)
    - Histologic pattern of injury
      - Dilation of portal veins and capillaries with endothelial hypertrophy
      - Monocytic, eosinophilic or neutrophilic microvasculitis (h-score 1: 3-4 marginated or intraluminal cells; 2: 5-10 cells; 3: > 10 cells)
      - Portal edema, ductular reaction
      - Cholestasis is usually present, but variable
      - Periportal hepatocyte necrosis may be prominent in ABO-incompatible grafts
      - Variable lymphocytic &/or necrotizing arteritis
    - Positive serum DSA
    - Diffuse C4d deposition (C4d-score 3: > 50%)
      - Staining portal stroma in ABO-incompatible grafts

- Strong linear/granular staining of endothelial cells lining portal veins and capillaries, hepatic arteries, sinusoids, and/or central veins
      - C4d score 0: negative; 1: minimal (< 10% portal tracts); 2: focal (10-50%); 3: diffuse (> 50%)
    - Reasonable exclusion of other insults that might cause similar injury
  - Suspicious (both following criteria required)
    - Positive serum DSA
    - C4d core + H-score = 3 or 4
  - Indeterminate (requires following first 2 + 3 or 4)
    - C4d-score + H-score ≥ 2
    - DSA is not available, equivocal, or negative
    - C4d is not available, equivocal, negative
    - Coexisting insult might be contributing to similar injury
- Chronic AMR (Banff criteria 2016)
  - Probable (all following 4 criteria required)
    - Histologic pattern of injury
      - Unexplained, at least mild portal &/or perivenular mononuclear cell inflammation with interface &/or perivenular activity
      - At least moderate portal/periportal, sinusoidal &/or perivenular fibrosis
    - Recent (< 3 months) positive serum DSA
    - At least focal C4d deposition in portal microvasculature
    - Reasonable exclusion of other insults that might cause similar injury
  - Possible
    - As above, but C4d is minimal or absent
- Frequent overlap with T-cell-mediated rejection

ANCILLARY TESTS

C4d Immunohistochemistry

- Specificity under further investigation
  - May or may not correlate with DSA
  - Can be difficult to interpret due to high background

DIFFERENTIAL DIAGNOSIS

Vascular Thrombosis

- Zone 3 hepatocyte damage

Preservation Injury

- Zone 3 hepatocyte damage

Biliary Obstruction

- Cholangiography is diagnostic
- More pronounced ductular reaction and fibrosis

Preservation Injury

- Zone 3 hepatocyte damage
- Progressive resolution

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Severe graft dysfunction immediately or during 1st week following revascularization

Pathologic Interpretation Pearls

- Massive hemorrhagic necrosis and thrombosis

SELECTED REFERENCES

1. Del Bello, A, et al. Donor-specific antibodies and liver transplantation. *Hum Immunol*. 2016. [ePub].
2. Demetris, AJ, et al. 2016 comprehensive update of the banff working group on liver allograft pathology: introduction of antibody-mediated rejection. *Am J Transplant*. 2016. [ePub].

Acute Cellular Rejection

KEY FACTS

Terminology

- Immune-mediated inflammation and injury of liver allograft due to genetic mismatch

Etiology/Pathogenesis

- Inflammatory cells in portal tracts and centrilobular, perivenular areas cause damage to biliary epithelium and endothelial cells

Clinical Issues

- Often asymptomatic but may present with fever or abdominal pain
- Nonspecific elevation of liver function tests
- Can occur at any time after transplantation but most often presents within 1st month
- General strategy is to increase immunosuppression
- If untreated, leads to chronic rejection and allograft failure
- Prognosis is very good if recognized and treated

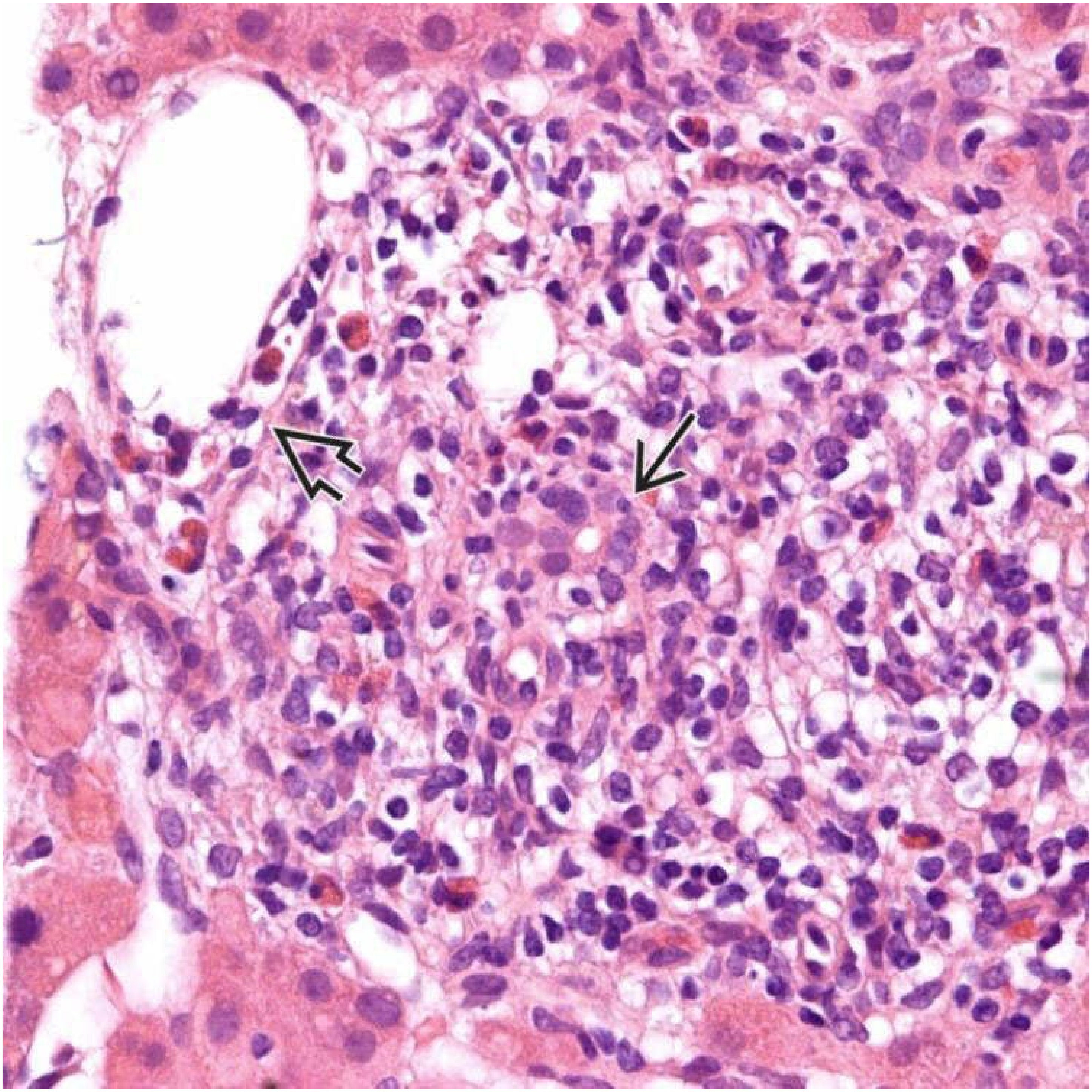
Microscopic

- Mixed portal inflammatory cell infiltrates
  - Enlarged, activated, or blastic T lymphocytes, eosinophils, and other inflammatory cells
- Bile duct damage
  - Lymphocytic infiltration and epithelial cell injury affecting interlobular ducts
- Endotheliitis
  - Subendothelial venous inflammation with lifting and denudation of endothelial cells

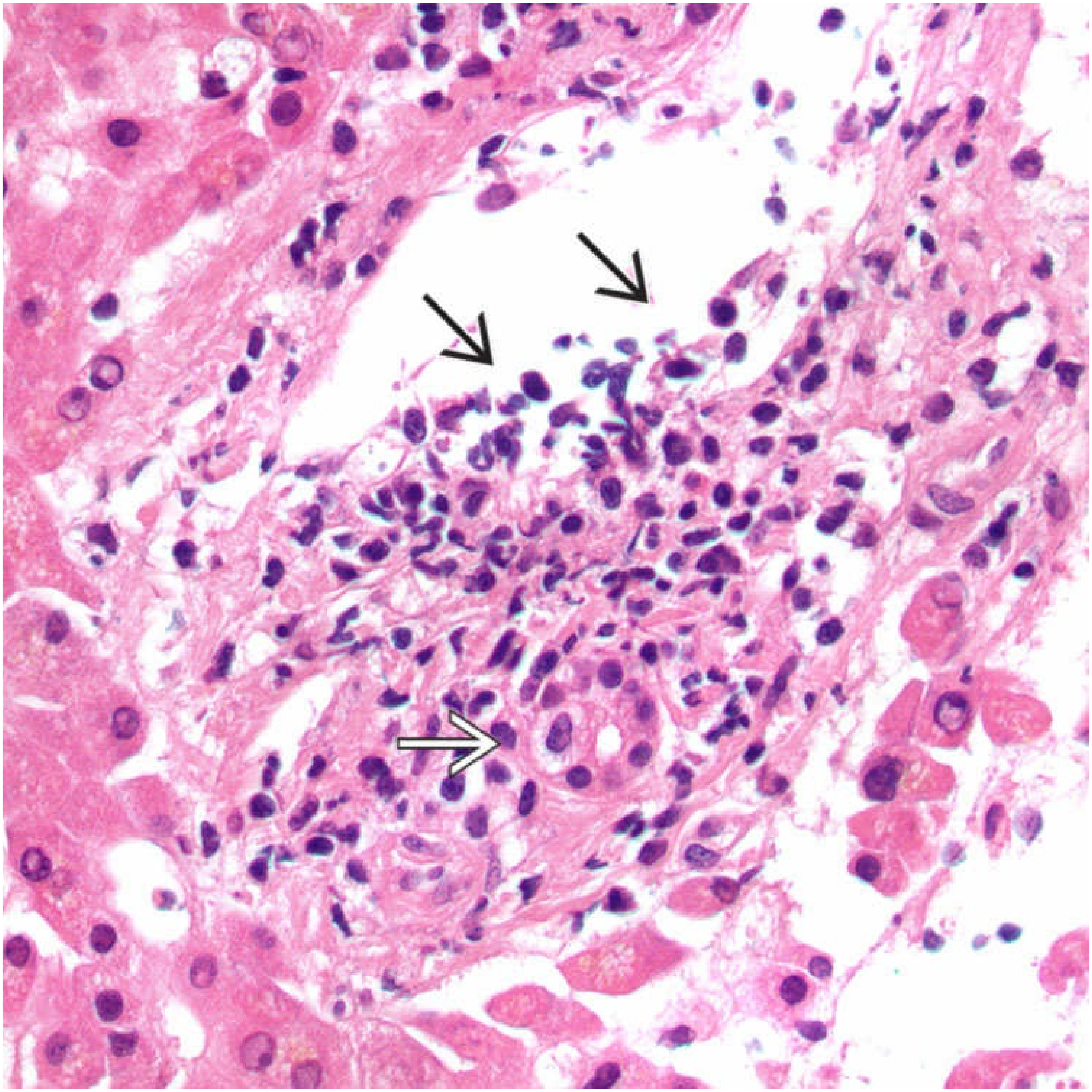
Top Differential Diagnoses

- Recurrent chronic viral hepatitis (hepatitis B or hepatitis C)
- Biliary complications

• Autoimmune hepatitis
• Posttransplant lymphoproliferative disorders

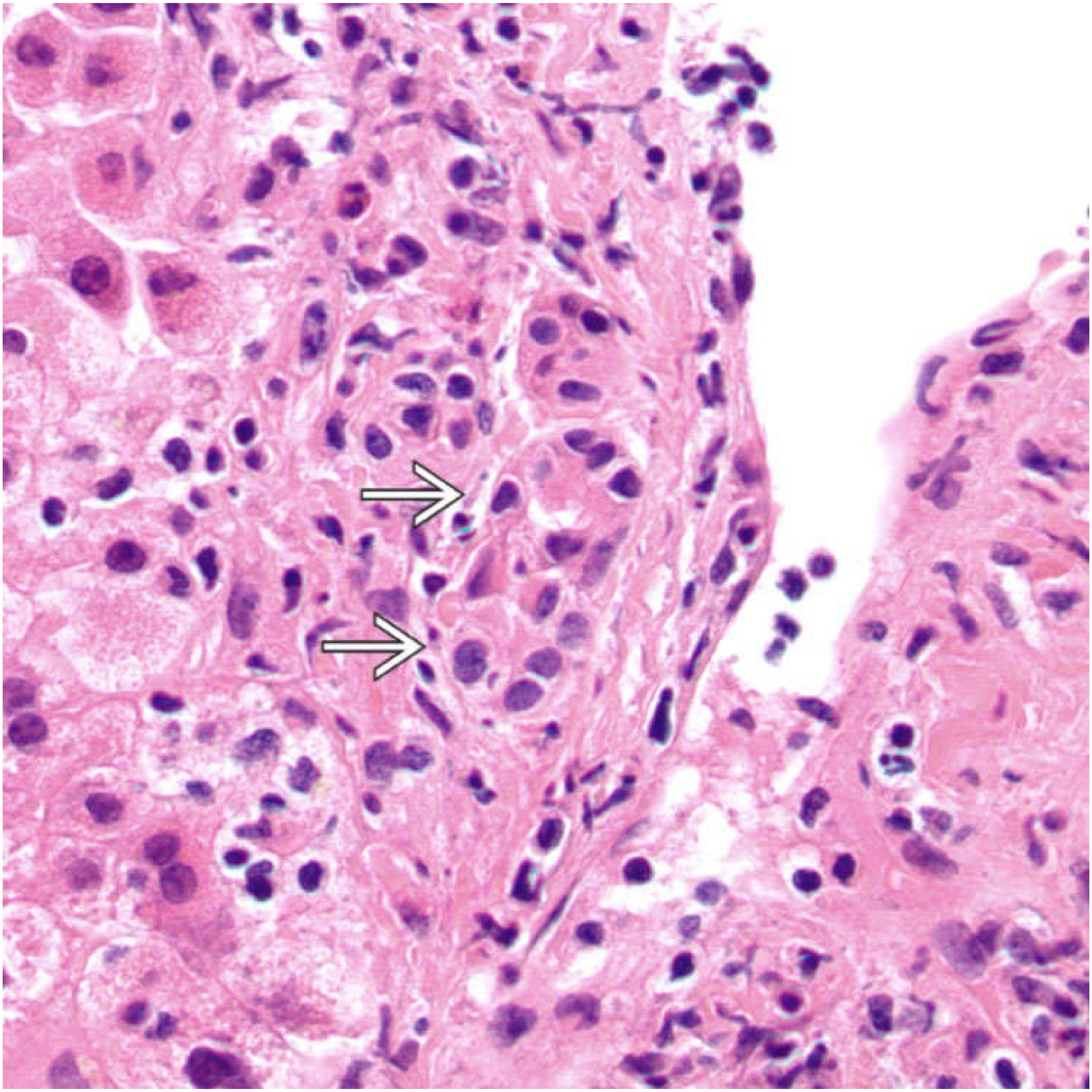


Classic Features of Rejection
This portal tract contains a mixed inflammatory infiltrate with activated lymphocytes, eosinophils, and plasma cells. The bile duct shows lymphocytic cholangitis and epithelial disarray →. The portal venule contains endotheliitis ⇨ .



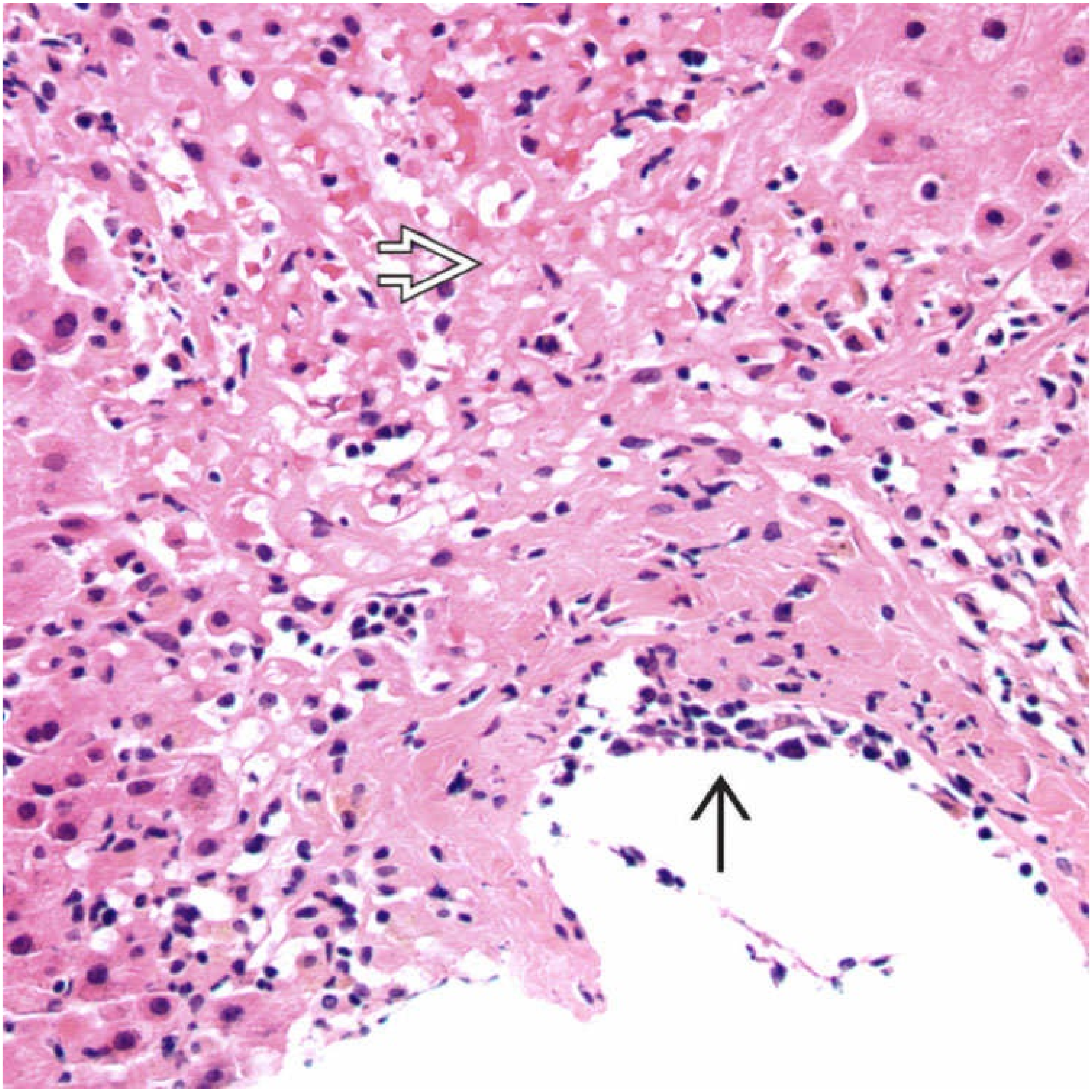
Portal Vein Endotheliitis

Endotheliitis → is present in a portal vein branch, characterized by inflammatory cells undermining the endothelium and lifting it up. The portal tract also contains a mild inflammatory cell infiltrate, and there is mild bile duct damage ⇨ .



Bile Duct Damage

Bile duct damage ⇨ is seen in a case of acute cellular rejection. The bile duct epithelial cells show nuclear hyperchromasia, pleomorphism, uneven spacing of nuclei, and loss of polarity. The portal tract also contains a mixed inflammatory cell infiltrate.



Endotheliitis and Perivenular Necrosis
Endotheliitis → affects a terminal hepatic vein. There is also perivenular hepatocyte necrosis ⇨ in this case of severe acute rejection.

TERMINOLOGY

Abbreviations

• Acute cellular rejection (ACR)

Definitions

• Immune-mediated inflammation and injury of liver allograft due to genetic mismatch

ETIOLOGY/PATHOGENESIS

Immune-Mediated Inflammatory Process

- Recipient immune system recognizes donor antigens in liver allograft as foreign
- Inflammatory cells in portal tracts and centrilobular, perivenular areas cause damage to biliary epithelium and endothelial cells

CLINICAL ISSUES

Epidemiology

- Incidence
  - Affects ~ 20-40% of liver allograft recipients
  - All liver transplant recipients are susceptible
    - More frequent in younger, healthier recipients and with older donors, long cold ischemia time, and immune dysregulation of recipient

Presentation

- Often asymptomatic
- May present with fever, hepatomegaly, ascites, abdominal pain

Laboratory Tests

- Nonspecific elevation of transaminases, bilirubin, alkaline phosphatase, &/or γ-glutamyl transferase

Natural History

- If untreated, leads to chronic rejection and allograft failure

Treatment

- Drugs
  - General strategy is to increase immunosuppression
  - Corticosteroids are standard therapy
  - May be managed by adjusting baseline immunosuppression or adding other immunosuppressants

Prognosis

- Very good if recognized and treated

Timing

- Any time after transplantation but most often presents within 1st month

MICROSCOPIC

Histologic Features

- Mixed portal inflammatory cell infiltrates
  - Mixture of enlarged, activated, or blastic lymphocytes, eosinophils, neutrophils, and macrophages
  - Inflammation predominantly composed of CD8(+) T lymphocytes
- Bile duct damage and inflammation
  - Lymphocytic infiltration of interlobular bile ducts (lymphocytic cholangitis)
  - Irregular shape and spacing of epithelial nuclei, cytoplasmic eosinophilia and vacuolization, apoptosis
- Subendothelial venous inflammation of portal &/or hepatic veins (endotheliitis)
  - Venous inflammation with lifting and denudation of endothelial cells
  - In severe ACR, associated with perivenular parenchymal necrosis
  - Rarely affects hepatic arterioles
- At least 2 of these 3 features support diagnosis of ACR
  - Must exclude other diseases
- Necrotizing arteritis is rarely sampled on needle biopsy
- Central perivenulitis (perivenular inflammation and hepatocyte dropout) may occur with typical portal features of ACR **or** as isolated finding
- Banff grading based on global assessment
  - Mild: Minority of portal tracts involved by generally mild infiltrates confined to portal tracts
  - Moderate: Majority of portal tracts involved
  - Severe: Features of moderate ACR plus spillover of inflammation into perivenular and periportal areas with perivenular hepatocyte necrosis

DIFFERENTIAL DIAGNOSIS

Recurrent Chronic Viral Hepatitis (Hepatitis B or Hepatitis C)

- Need clinical history of chronic viral hepatitis
  - Both ACR and chronic viral hepatitis exhibit portal inflammation and can show endotheliitis
  - More mononuclear portal inflammatory cell infiltrate, interface activity, and foci of lobular inflammation favor chronic viral hepatitis
  - Late ACR can show fewer blastic lymphocytes, less endotheliitis, and more lobular inflammation

Biliary Complications

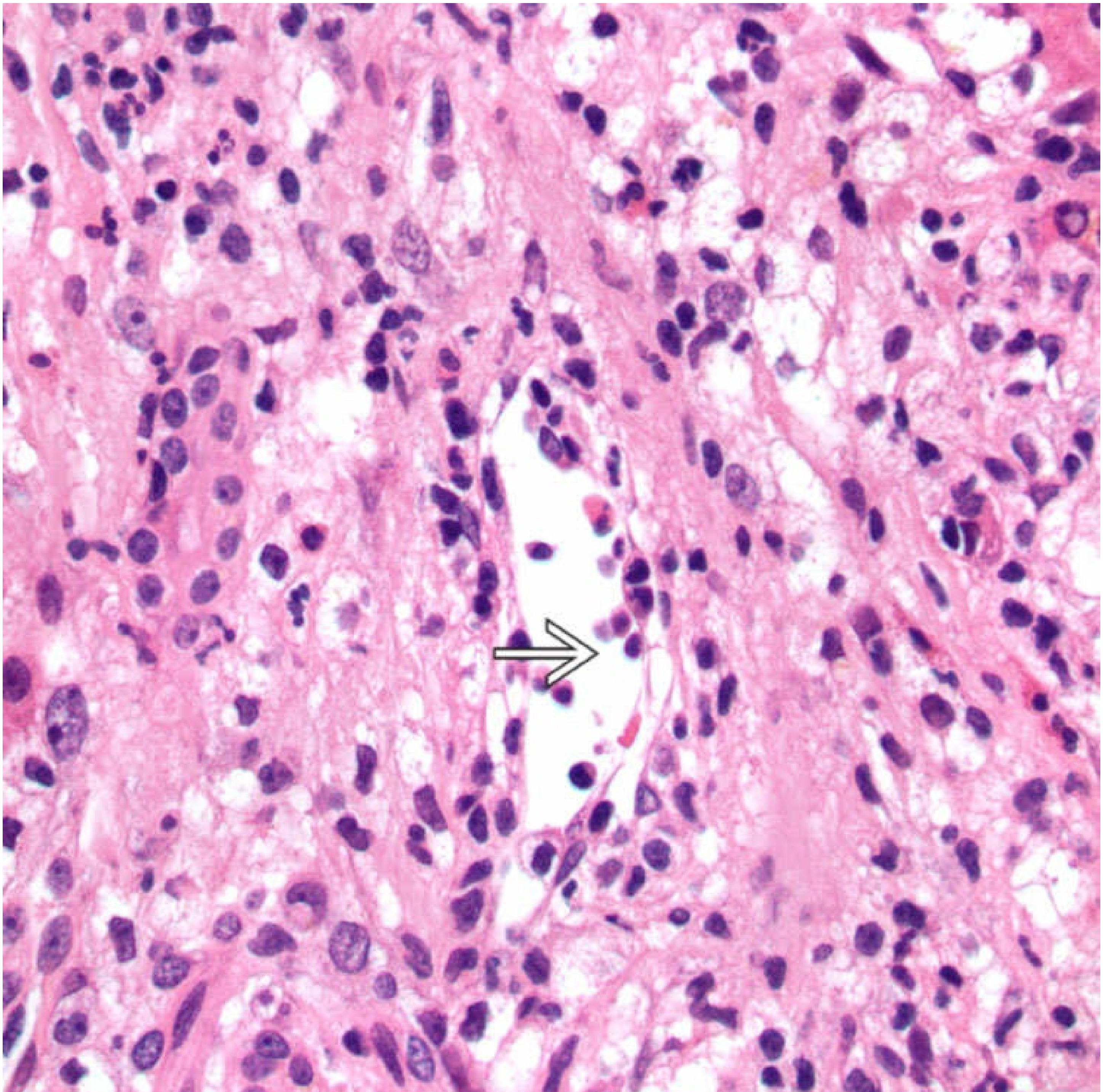
- More neutrophil-rich portal inflammatory cell infiltrates, bile ductular proliferation, and may show portal edema
- Acute cholangitis shows collections of neutrophils within bile duct lumina

Autoimmune Hepatitis

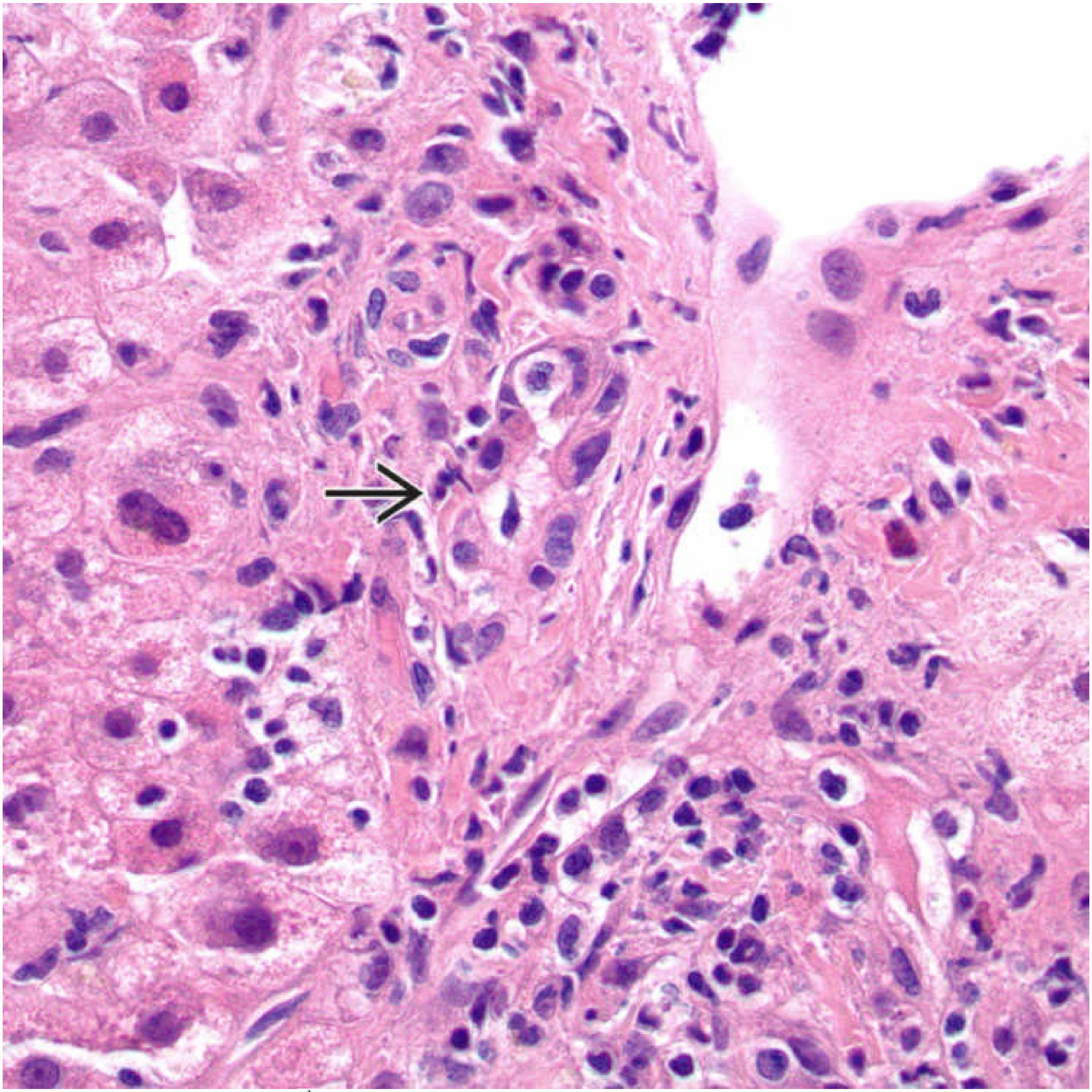
- De novo or recurrent autoimmune hepatitis usually exhibits numerous plasma cells, more centrilobular perivenular inflammation, and more interface hepatitis

Posttransplant Lymphoproliferative Disorders

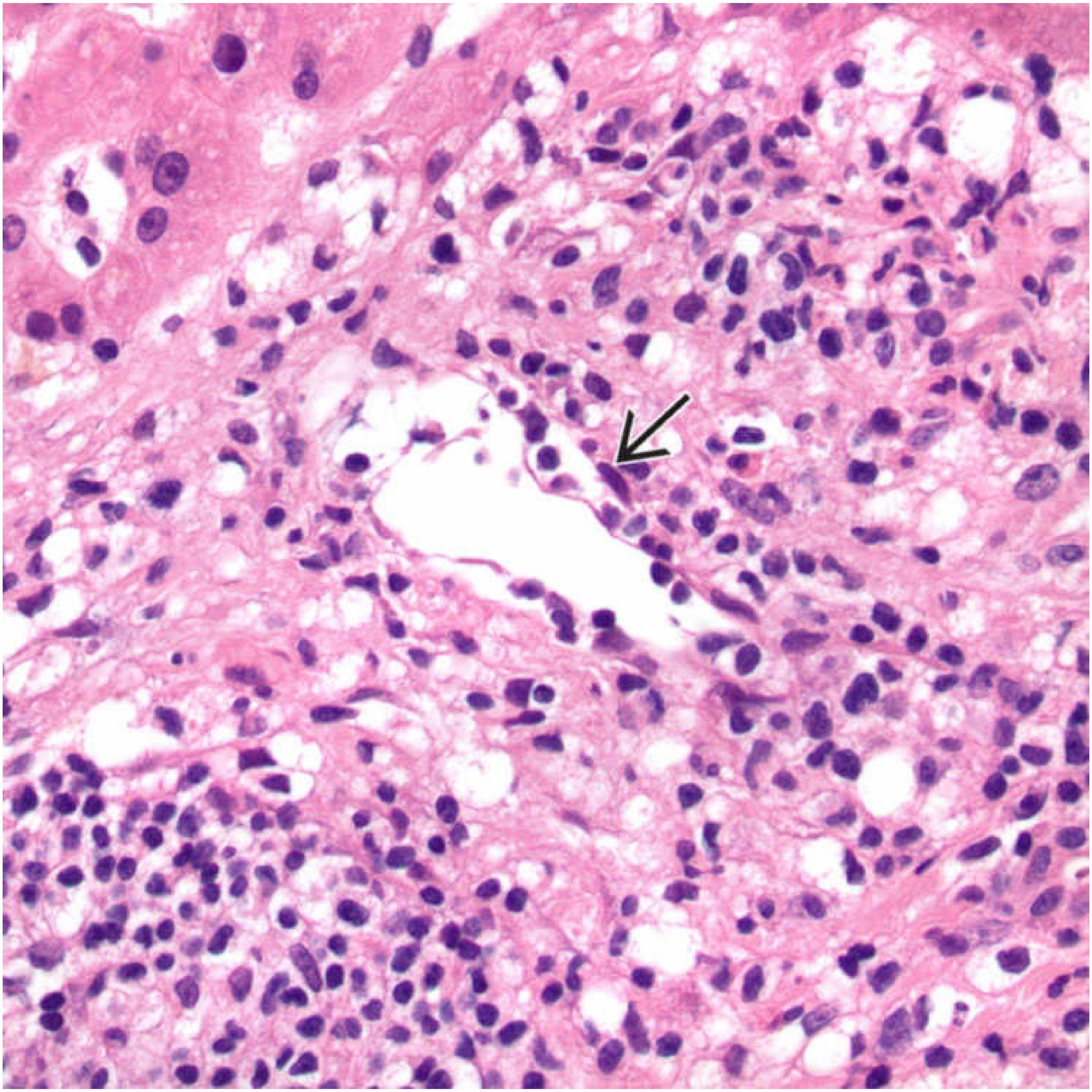
• Vast majority are B-cell processes, whereas ACR exhibits mostly T lymphocytes



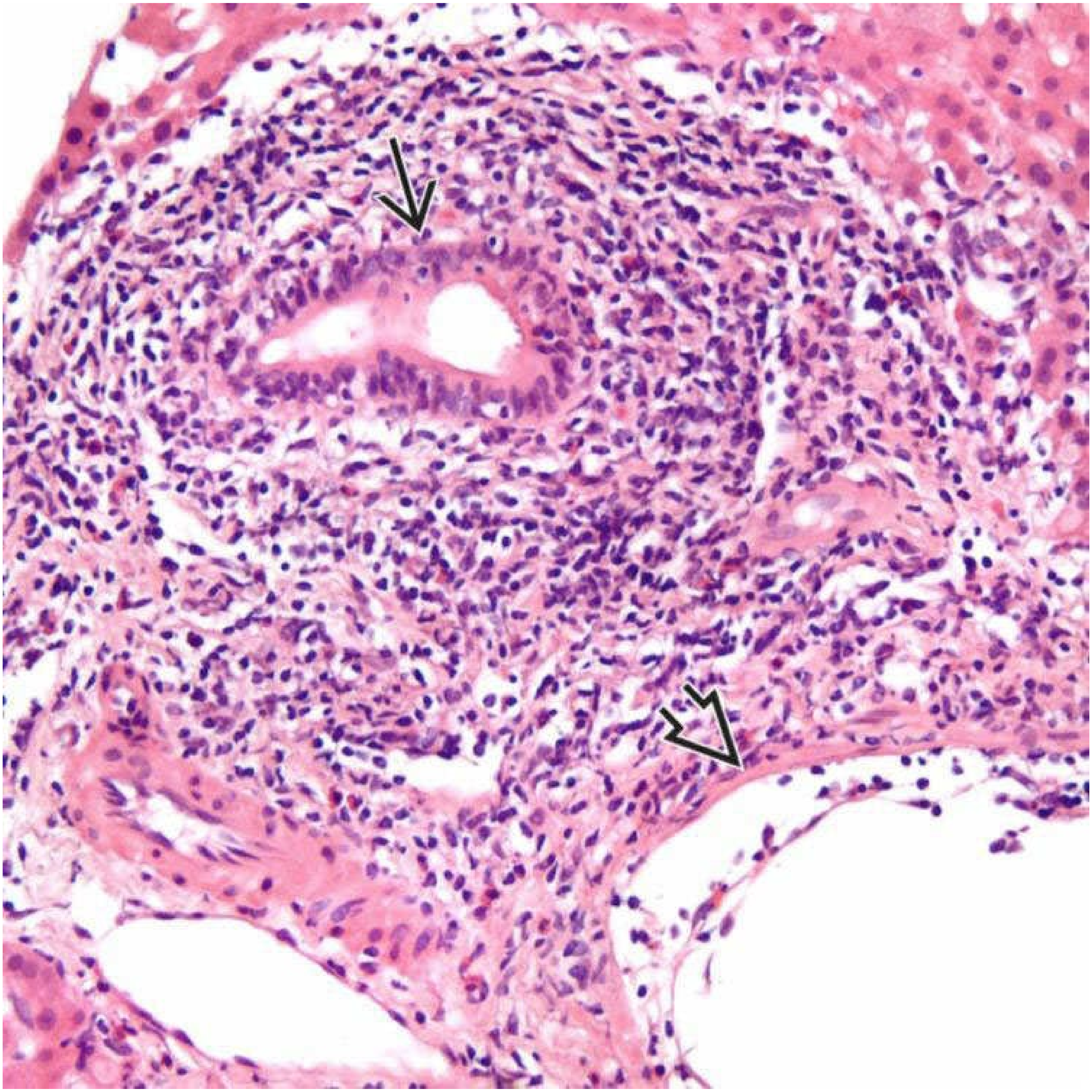
Endotheliitis is characterized by inflammation of the vein wall and associated endothelial cell lifting .



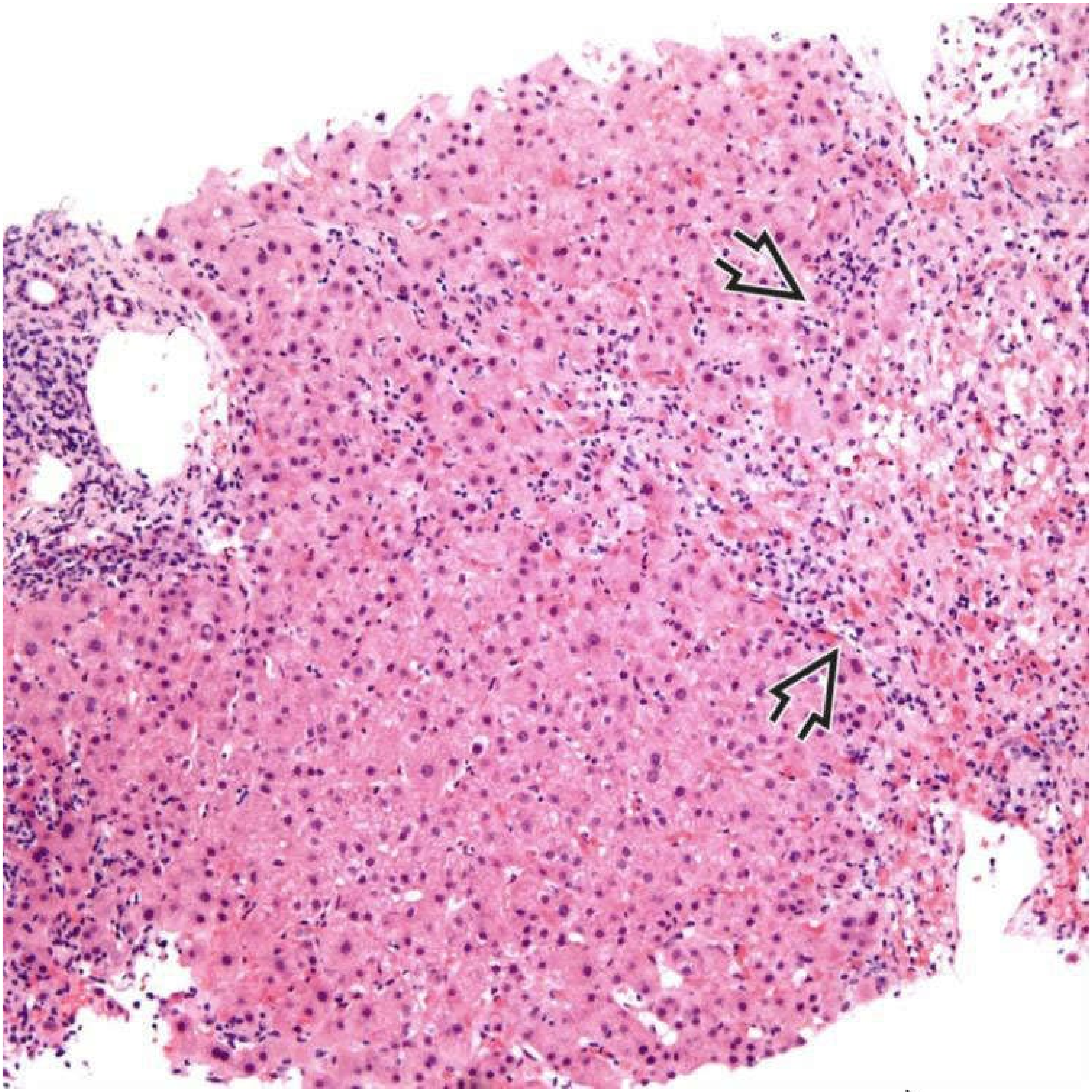
This damaged duct → shows loss of nuclear polarity, cytoplasmic vacuolization, and nuclear hyperchromasia.



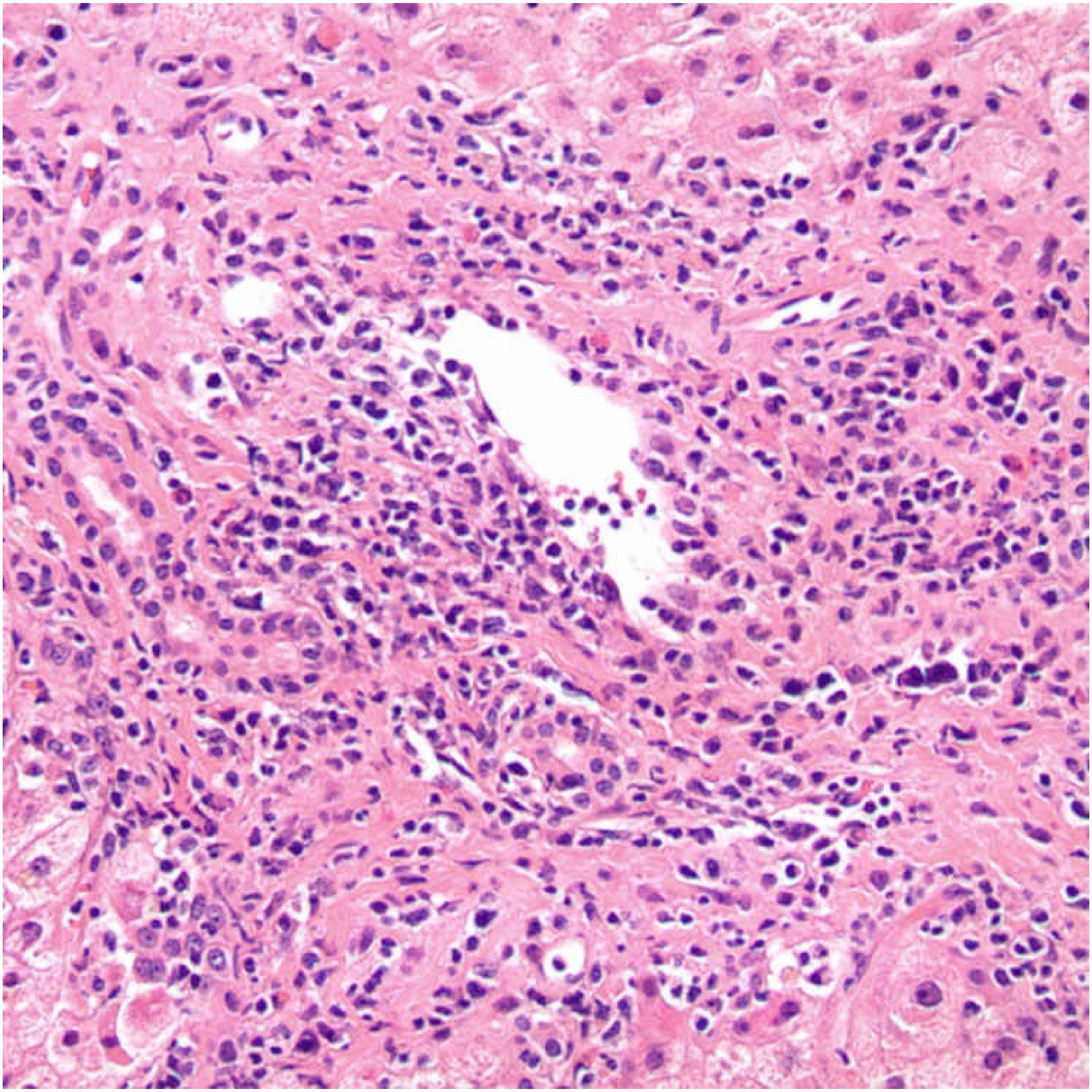
This case of acute cellular rejection shows a mixed portal infiltrate with a venule showing endotheliitis in the center of the field. Note the inflammatory cells underneath the epithelium, lifting it up →.



The portal tract contains a mixed inflammatory infiltrate predominantly consisting of lymphocytes and eosinophils. There is lymphocytic cholangitis →. Note the endotheliitis in the lower right corner ⇨ .



The portal tract at the left contains a mixed infiltrate. The pericentral (zone 3) parenchyma ➭ is necrotic with associated lymphocytic inflammation.



A mixed portal inflammatory cell infiltrate composed of activated-appearing lymphocytes, histiocytes, eosinophils, and other inflammatory cells is typical of acute cellular rejection.

SELECTED REFERENCES

1. Moreira, RK. Recurrent hepatitis C and acute allograft rejection: clinicopathologic features with emphasis on the differential diagnosis between these entities. *Adv Anat Pathol*. 2011; 18(5):393–405.
2. Neil, DA, et al. Current views on rejection pathology in liver transplantation. *Transpl Int*. 2010; 23(10):971–983.
3. Hübscher, SG. Transplantation pathology. *Semin Liver Dis*. 2009; 29(1):74–90.
4. Banff Working Group, et al. Liver biopsy interpretation for causes of late liver allograft dysfunction. *Hepatology*. 2006; 44(2):489–501.

Chronic Rejection

KEY FACTS

Classification

- Obliterative (foam cell) arteriopathy
- Bile duct loss

Etiology/Pathogenesis

- May evolve from severe or repeated acute cellular rejection and result in potentially irreversible damage to interlobular bile ducts &/or endothelium of veins and arteries

Clinical Issues

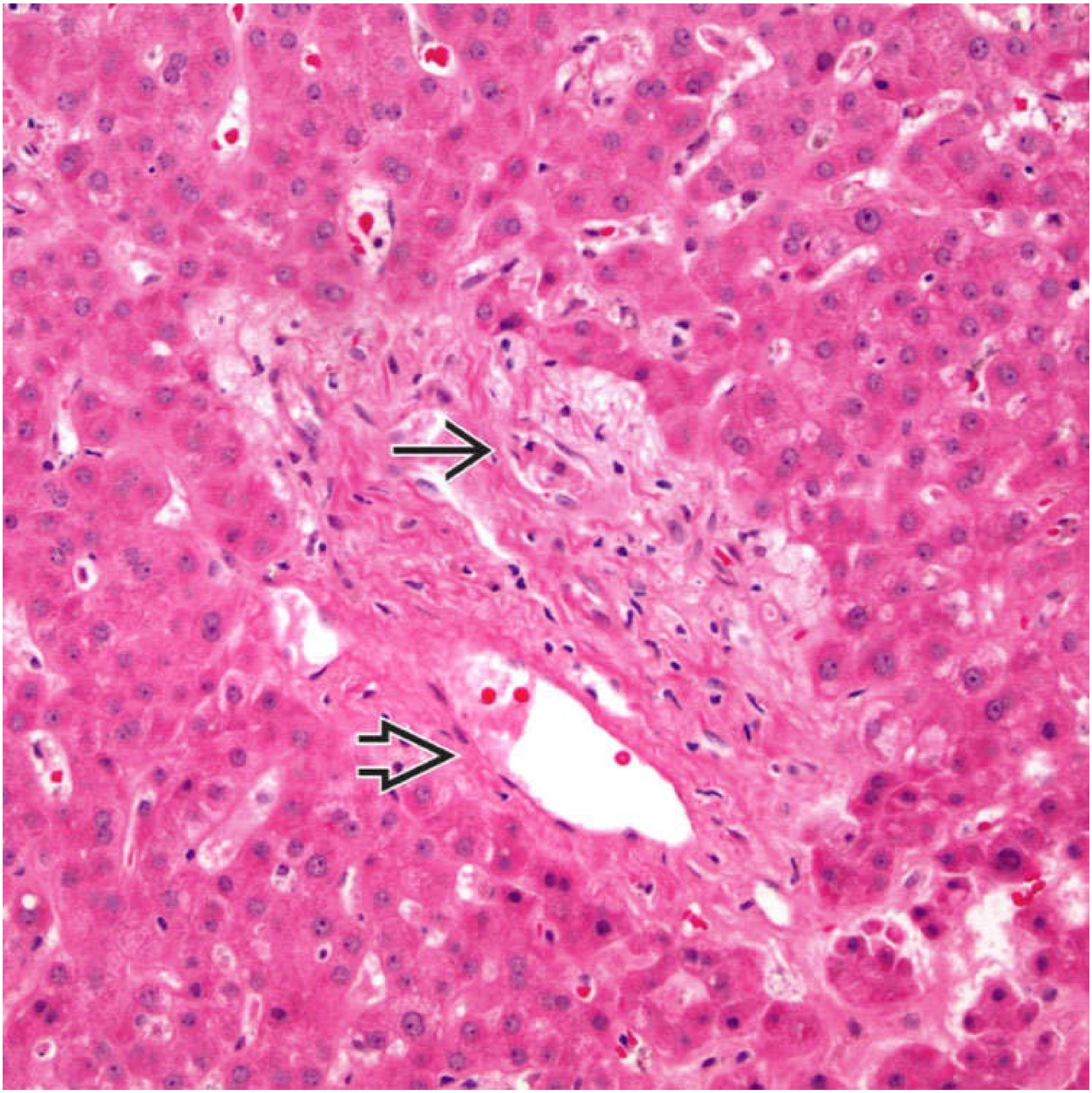
- Progressive jaundice and elevated cholestatic enzymes
- Early chronic rejection may respond to potent immunosuppressants such as tacrolimus, OKT3, mycophenolate, or rapamycin
- Usually unresponsive to immunosuppression
- Retransplantation often needed

Microscopic

- Atypical bile duct epithelium resembling dysplasia
- Centrizonal perivenular hepatocyte dropout in early phase
- Loss of interlobular bile duct in late phase
- Loss of hepatic arteries in late phase
- Foam cell arteriopathy
- Luminal narrowing by subintimal foam cells
- > 50% of portal tracts do not have interlobular bile ducts
- Cholestasis often prominent
- Ductular reaction, periportal fibrous expansion usually absent
- Portal inflammation typically decreases over time
- Reviewing serial previous biopsies may be necessary
- PAS-D, CK7, or CK19 may help identify bile ducts

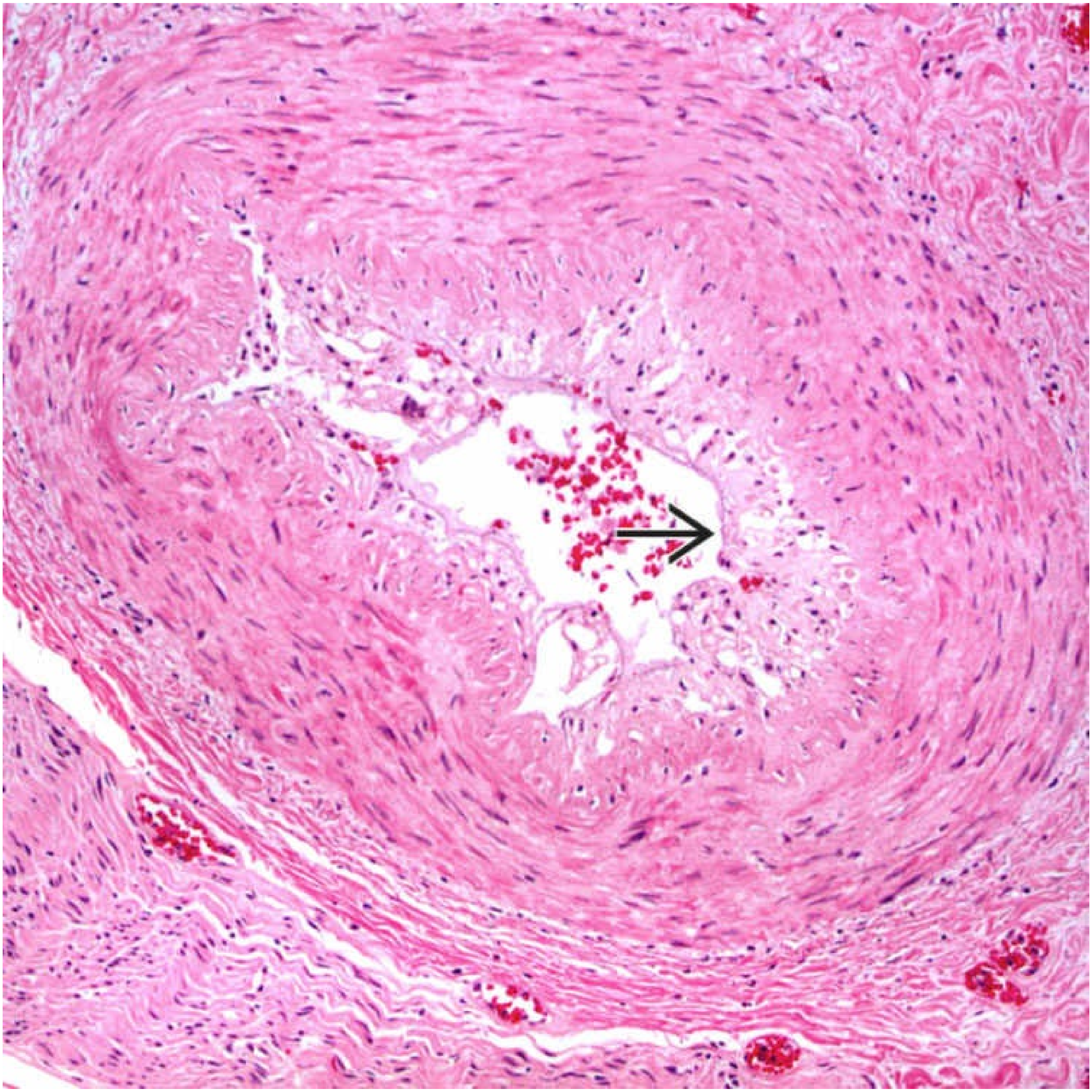
Top Differential Diagnoses

- Ischemic cholangiopathy
- Recurrent primary biliary cholangitis
- Recurrent primary sclerosing cholangitis
- Vanishing bile duct syndrome in drug-induced liver disease

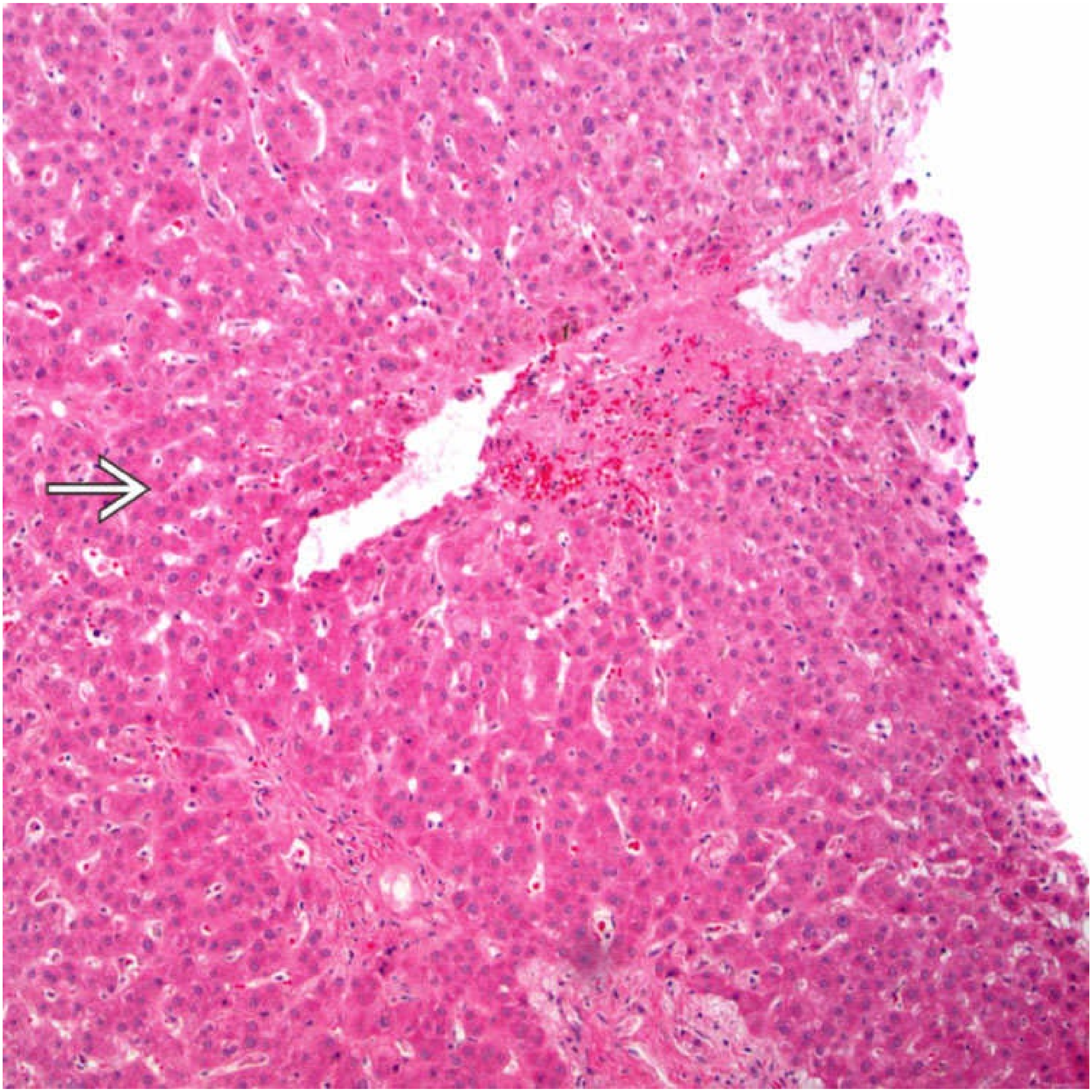


Portal Tract Showing Paucity of Bile Ducts

Portal tract in a case of chronic ductopenic rejection contains a hepatic artery → and portal vein ⇨ but no interlobular bile duct.

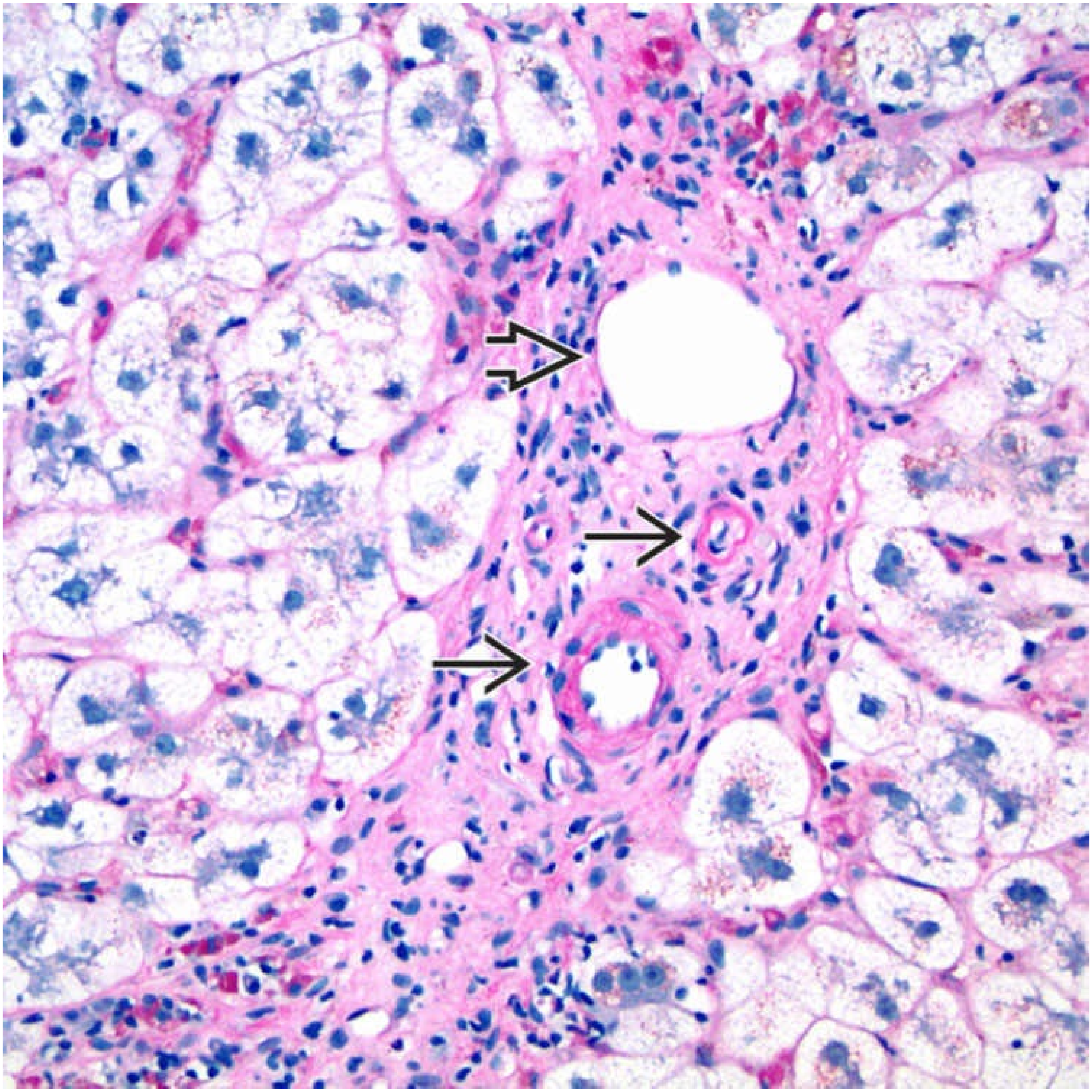


Intimal Foam Cell Arteriopathy
Medium-sized muscular artery shows intimal foam cell arteriopathy → in chronic rejection.



Hepatocellular Necrosis in Early Chronic Rejection

Centrilobular hepatocellular necrosis ⇨ may be an early sign of impending chronic rejection.



PAS-D Highlights Paucity of Bile Ducts
PAS stain with diastase digestion in a case of chronic rejection shows the presence of hepatic arterioles → and portal vein ⇨ but no interlobular bile ducts.

TERMINOLOGY

Abbreviations

- Chronic rejection (CR)

Synonyms

- Ductopenic rejection

Definitions

- Presents in 2 forms
  - Obliterative (foam cell) arteriopathy
    - – Only seen in large- and medium-sized arteries
  - Bile duct loss
    - – Most common finding in allograft biopsy

ETIOLOGY/PATHOGENESIS

Immune-Mediated Damage to Allograft

- May evolve from severe or repeated acute cellular rejection and result in potentially irreversible damage to interlobular bile ducts &/or endothelium of veins and arteries
- Occurs later than acute cellular rejection

CLINICAL ISSUES

Presentation

- Progressive jaundice and elevated cholestatic enzymes

Treatment

- Early chronic rejection may respond to potent immunosuppressants such as tacrolimus, OKT3, mycophenolate, or rapamycin

Prognosis

- Usually unresponsive to immunosuppression
- Retransplantation often needed

MICROSCOPIC

Histologic Features

- Early chronic rejection
  - Lymphocytic cholangitis
  - Atypical bile duct epithelium; may resemble dysplasia
  - Centrizonal perivenular hepatocyte dropout
- Late chronic rejection
  - Loss of interlobular bile ducts
  - Loss of hepatic arteries
  - Foam cell arteriopathy with luminal narrowing by subintimal foam cells
  - Portal inflammation typically decreases over time

    - Perivenular necrosis is common
- Ductopenic rejection
    - > 50% of portal tracts do not have interlobular bile ducts
    - Sufficient number of portal tracts need to be present in biopsy for evaluation (ideally > 20)
    - Reviewing serial previous biopsies may be necessary
    - PAS-D, CK7, or CK19 may help identify bile ducts when ductopenia is suspected
    - Cholestasis often prominent
    - Ductular reaction, periportal fibrous expansion usually absent
    - Marked perivenular fibrosis with bridging may develop in late chronic rejection

DIFFERENTIAL DIAGNOSIS

Ischemic Cholangiopathy

- Imaging studies may help
- CR usually lacks secondary biliary features such as ductular reaction, copper staining

Recurrent Primary Biliary Cholangitis

- Florid duct lesions, portal inflammation, and bile ductular reaction
- Positive antimitochondrial antibody (AMA)

Recurrent Primary Sclerosing Cholangitis

- Characteristic ERCP findings
- Sclerosing ducts
- Portal inflammation with bile ductular reaction

Drug-Induced Vanishing Bile Duct Syndrome

- History of medications known to cause ductopenia
    - Augmentin
    - Chlorpromazine
    - Phenytoin

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Previous episodes of severe or persistent acute cellular rejection

Pathologic Interpretation Pearls

- Centrilobular necrosis &/or cholestasis in repeated biopsy specimens should be considered warning sign of possible chronic rejection

• Foam cell arteriopathy typically occurs in medium- or large-sized arteries and is seldom seen in allograft biopsy specimens

SELECTED REFERENCES

1. Neil, DA, et al. Current views on rejection pathology in liver transplantation. *Transpl Int*. 2010; 23(10):971–983.
2. Banff Working Group, et al. Liver biopsy interpretation for causes of late liver allograft dysfunction. *Hepatology*. 2006; 44(2):489–501.
3. Lefkowitch, JH. Diagnostic issues in liver transplantation pathology. *Clin Liver Dis*. 2002; 6(2):555–570. [ix].
4. Demetris, A, et al. Update of the International Banff Schema for Liver Allograft Rejection: working recommendations for the histopathologic staging and reporting of chronic rejection. An International Panel. *Hepatology*. 2000; 31(3):792–799.
5. Jones, KD, et al. Interpretation of biopsy findings in the transplant liver. *Semin Diagn Pathol*. 1998; 15(4):306–317.
6. Noack, KB, et al. Severe ductopenic rejection with features of vanishing bile duct syndrome: clinical, biochemical, and histologic evidence for spontaneous resolution. *Transplant Proc*. 1991; 23(1 Pt 2):1448–1451.
7. van Hoek, B, et al. Recurrence of ductopenic rejection in liver allografts after retransplantation for vanishing bile duct syndrome. *Transplant Proc*. 1991; 23(1 Pt 2):1442–1443.
8. Ludwig, J, et al. Persistent centrilobular necroses in hepatic allografts. *Hum Pathol*. 1990; 21(6):656–661.

Hepatic Artery Thrombosis

KEY FACTS

Terminology

- Thrombotic occlusion of hepatic artery &/or its branches

Etiology/Pathogenesis

- Secondary to atherosclerosis, hypercoagulable state, complication after liver transplantation, or infusion of chemotherapeutic agents
  - Results in bile duct ischemia, hepatic parenchymal infarction
  - – Bile ducts depend on arterial flow and therefore suffer ischemic injury

Clinical Issues

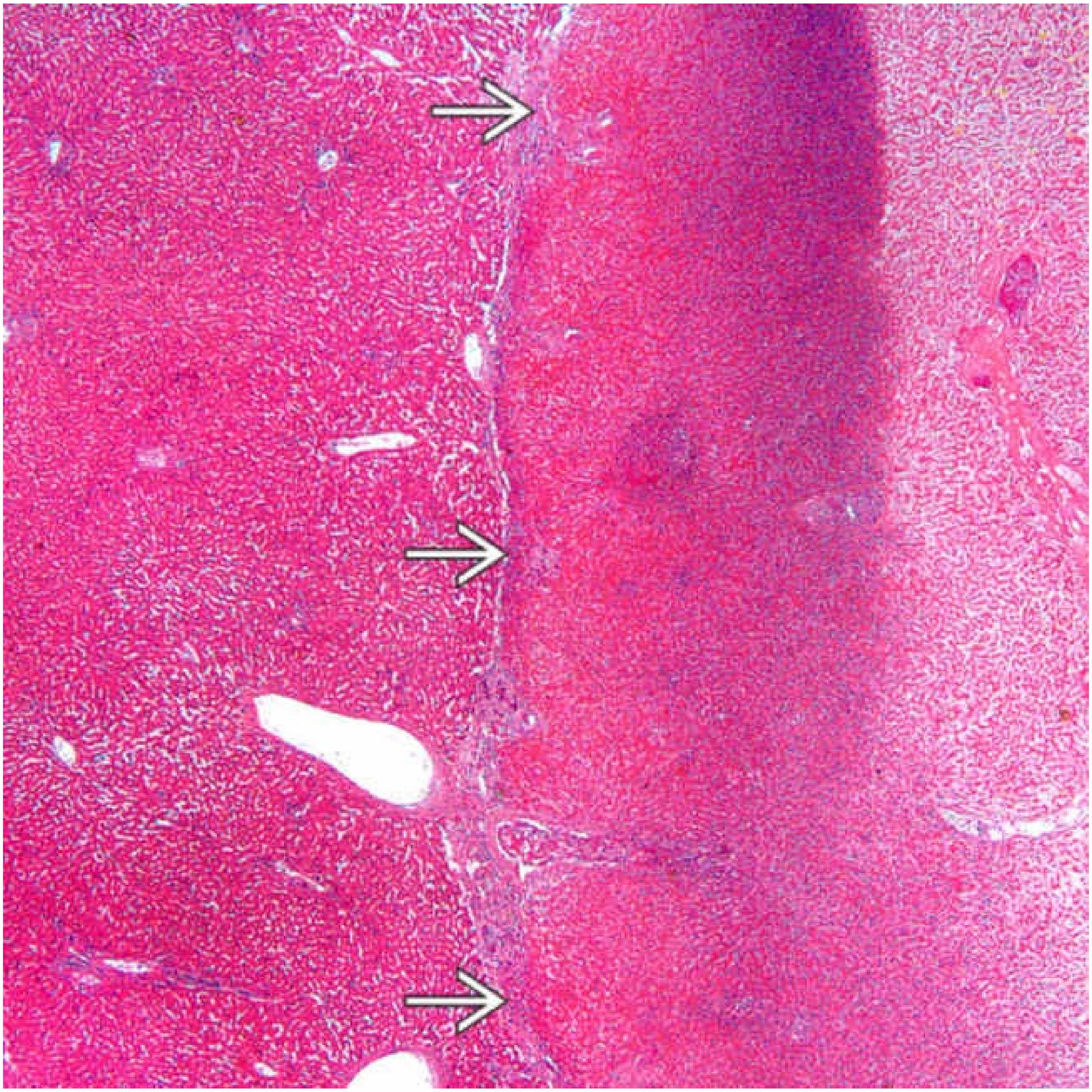
- Relatively well tolerated in native livers
  - Anastomosing blood supply with good collateralization protects against ischemic injury
- Transplanted livers much more susceptible, especially early post transplant
- Symptoms related to acuity and ensuing complications
- Cholestatic liver function abnormalities are common

Microscopic

- Zone 3 hemorrhage and hepatocyte dropout in early posttransplant period
  - Ischemic bile duct injury
  - Denuded, necrotic bile duct epithelium sloughs into lumen, forming eosinophilic bile casts
  - Bile leakage into periductal connective tissue
  - In time, chronic ischemia can lead to biliary strictures, fibrosis, and duct loss
- Hepatic infarction
  - Necrosis of hepatocytes and portal connective tissue

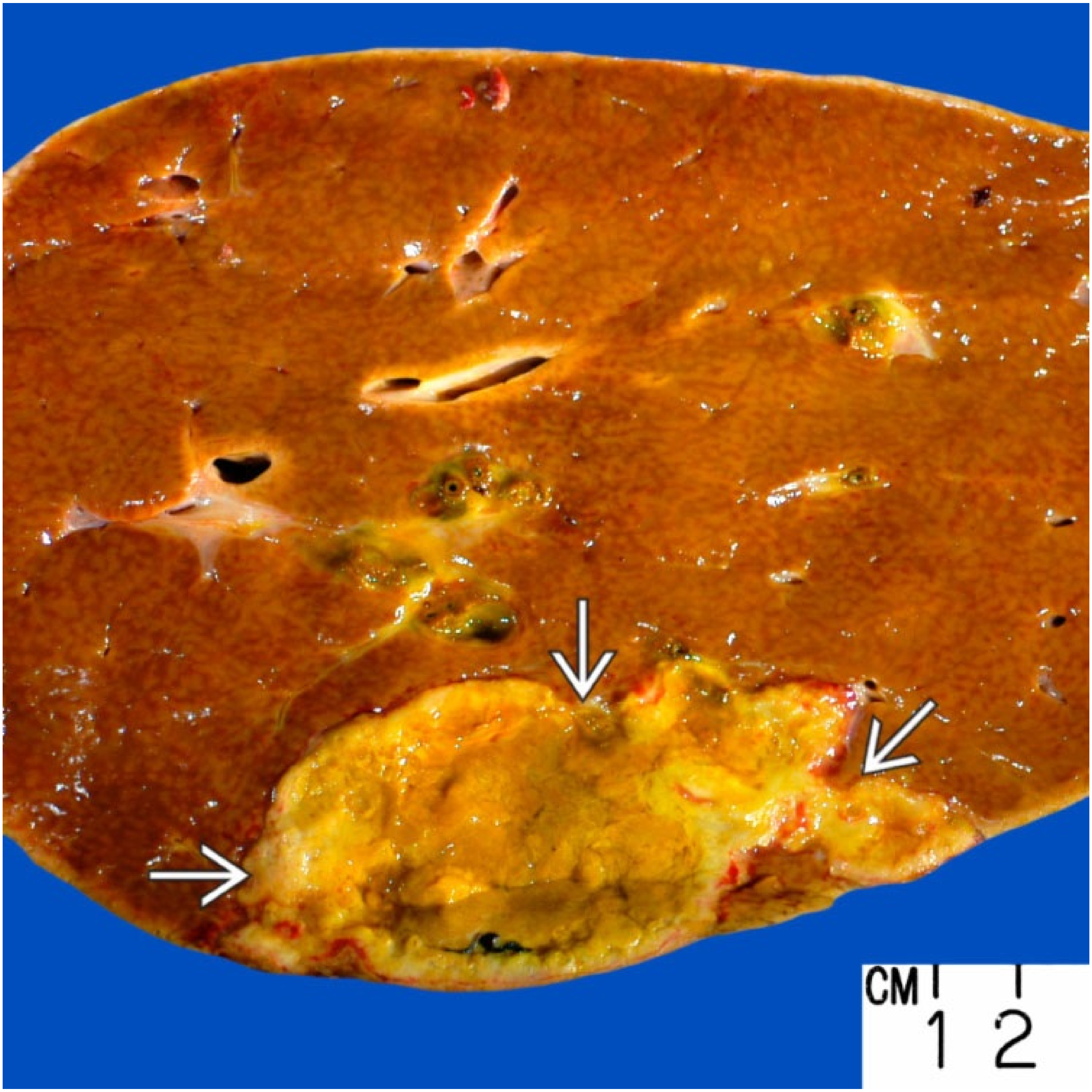
Diagnostic Checklist

• Needle biopsy may not be representative, as ischemic features may be patchy

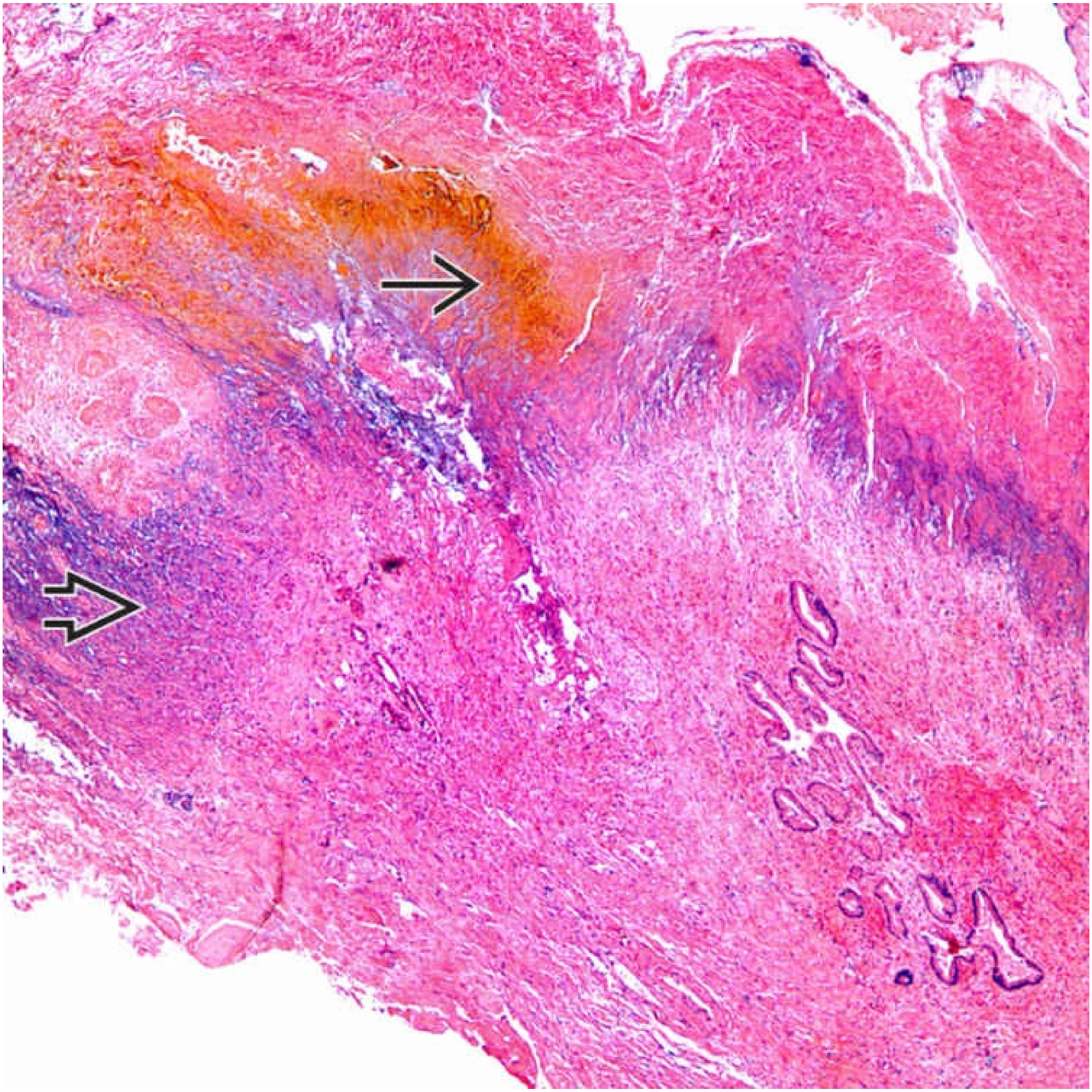


Hepatic Infarction

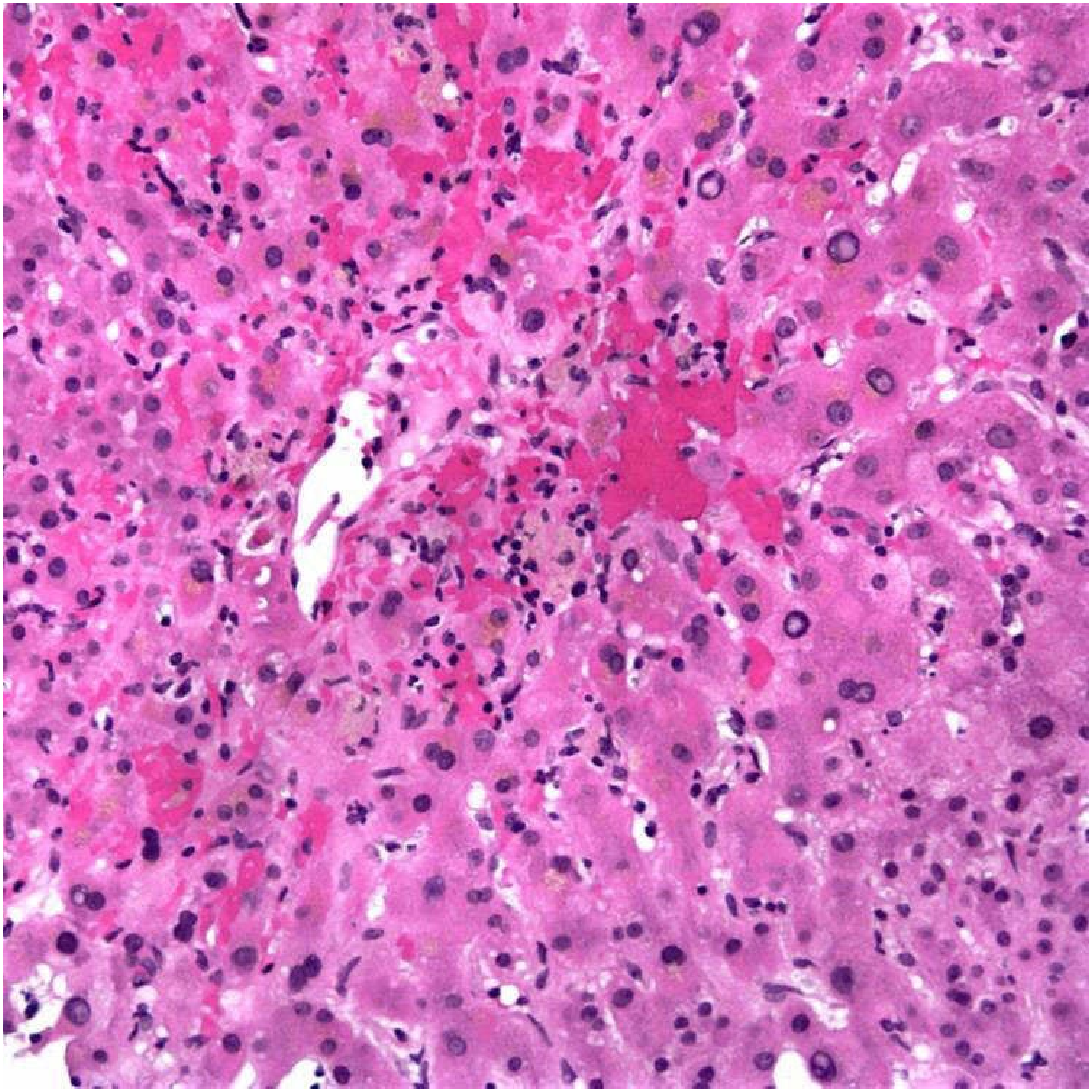
This section demonstrates a well-delineated area of hepatic parenchymal infarction ⇒ following hepatic artery thrombosis.



Abscess Due to Bile Duct Necrosis and Leak
An explanted allograft liver demonstrates an area of bile duct necrosis and a bile leak ⇒ in a patient who developed hepatic artery thrombosis after transplantation.



Bile Duct Necrosis and Leak
This large bile duct has suffered ischemic necrosis ⇨ and leakage of bile →. The bile duct ischemia occurred secondary to hepatic artery thrombosis.



Zone 3 Hemorrhage and Hepatocyte Dropout
Cases of hepatic artery thrombosis may feature nonspecific zone 3 hemorrhage, inflammation, and hepatocyte dropout, particularly early in the posttransplant course. These changes can mimic reperfusion injury.

TERMINOLOGY

Abbreviations

- Hepatic artery thrombosis (HAT)

Definitions

- Thrombotic occlusion of hepatic artery &/or its branches

ETIOLOGY/PATHOGENESIS

Causes of Thrombosis

- Atherosclerosis
  - Hypercoagulable state
  - Anastomotic complication after liver transplantation
  - ○ Greatest risk with nonheart-beating donors
- Hepatic artery infusion of chemotherapeutic agents

Sequelae

- Bile duct ischemia
  - ○ Bile ducts dependent on hepatic artery flow
  - – Acute ischemia leads to biliary ulcers, duct necrosis, and bile leaks
  - – Chronic ischemia leads to scarring, strictures, and duct loss
- Hepatic infarction

CLINICAL ISSUES

Epidemiology

- Incidence
  - ○ Relatively well tolerated in native livers
  - – Anastomosing blood supply with good collateralization is protective against ischemic injury

○ Transplanted livers much more susceptible, especially in early posttransplant period

– Most common cause of posttransplant vascular complications

– Liver grafts lack anastomosing blood supply and are more dependent on arterial inflow

– Pediatric and split-liver grafts at greatest risk due to smaller vessels and greater technical difficulty

Presentation

- Symptoms related to acuity and ensuing complications
  - ○ Fever
  - ○ Abdominal pain
  - ○ Jaundice
  - ○ Bile peritonitis
  - ○ Fulminant hepatic failure
- Cholestatic liver function abnormalities
  - ○ Elevated bilirubin, alkaline phosphatase, γ-glutamyl transferase

Treatment

- Surgical approaches
  - Arterial thrombectomy
  - Revascularization
  - Liver transplantation/retransplantation

Prognosis

- Long-term complications include ischemic cholangiopathy with stricture and duct loss
- Can lead to sepsis, fulminant hepatic failure, and multisystem organ failure

MACROSCOPIC

General Features

- May appear grossly normal, especially on surface
- Mottled liver parenchyma with foci of parenchymal necrosis and bile leak

MICROSCOPIC

Histologic Features

- Nonspecific zone 3 hemorrhage, inflammation, and hepatocyte dropout
  - Occurs very early in posttransplant period and mimics reperfusion injury
- Ischemic bile duct epithelial cell injury
  - Bile duct necrosis with flattening of epithelium and cytoplasmic eosinophilia
  - Eosinophilic bile casts comprised of sloughed, necrotic biliary epithelial cells
  - Bile leakage into periductal connective tissue
- Necrosis of hepatocytes and portal connective tissue seen in hepatic infarcts
  - May develop secondary infection and abscesses
- In time, ongoing ischemic injury can lead to biliary strictures, fibrosis, and duct loss

DIFFERENTIAL DIAGNOSIS

Primary Sclerosing Cholangitis

- May be indistinguishable from chronic ischemia based on histologic features alone
  - Distinct clinical picture
  - Typically young males with history of inflammatory bowel disease

Acute or Chronic Allograft Rejection

- Acute rejection shows typical rejection-type infiltrates and endotheliitis
- Chronic rejection shows senescent duct changes; associated with refractory or untreated acute rejection

Other Biliary Complications

- Biliary obstruction

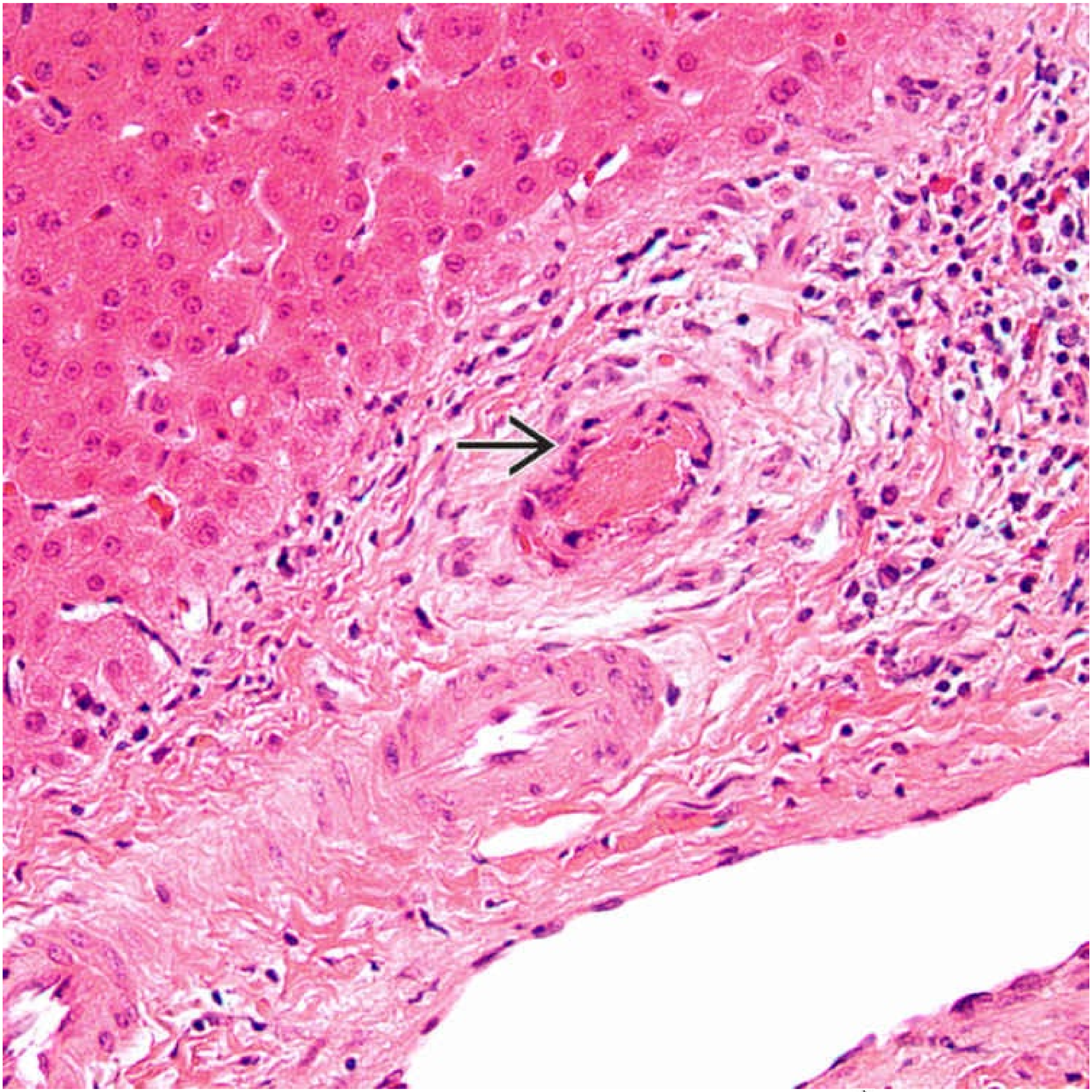
Ischemic Hepatitis

- More diffuse process with zone 3 hepatocyte injury

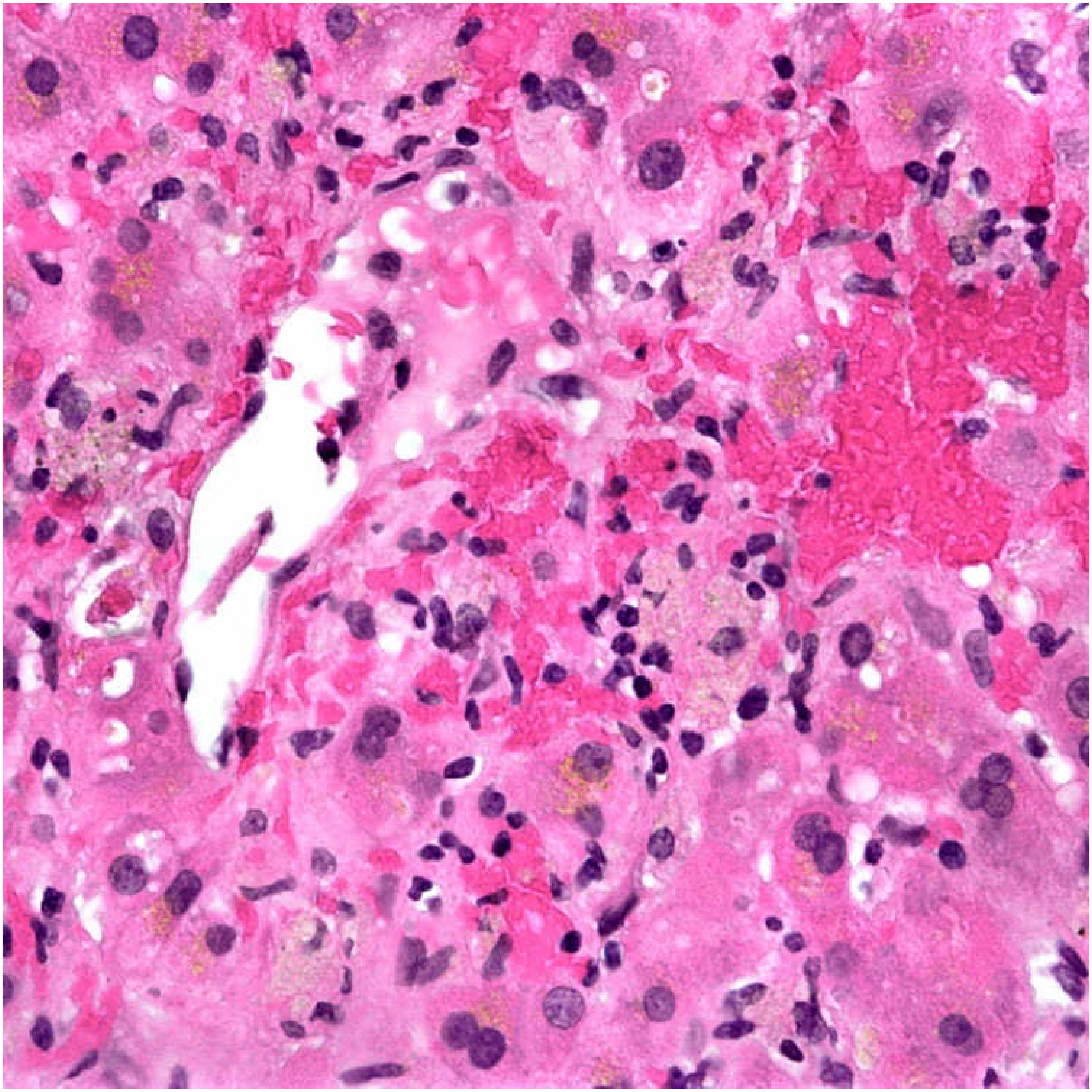
DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Ischemic features may be patchy, and large ducts often not sampled
  - Needle biopsy may not be representative



This example of hepatic artery thrombosis shows ischemic bile duct epithelial cell → injury with an intraluminal eosinophilic bile cast.



This liver biopsy shows zone 3 hemorrhage and hepatocyte dropout in a case of posttransplant hepatic artery thrombosis.

SELECTED REFERENCES

1. Mourad, MM, et al. Etiology and management of hepatic artery thrombosis after adult liver transplantation. *Liver Transpl*. 2014; 20(6):713–723.
2. Adeyi, O, et al. Liver allograft pathology: approach to interpretation of needle biopsies with clinicopathological correlation. *J Clin Pathol*. 2010; 63(1):47–74.
4. Deltenre, P, et al. Ischemic cholangiopathy. *Semin Liver Dis*. 2008; 28(3):235–246.

3. Bekker, J, et al. Early hepatic artery thrombosis after liver transplantation: a systematic review of the incidence, outcome and risk factors. *Am J Transplant*. 2009; 9(4):746–757.

Graft-vs.-Host Disease

KEY FACTS

Terminology

- Attack of immunocompetent, donor-derived cells against recipient tissues
- Usually occurs in bone marrow transplant or hematopoietic stem cell transplant recipients

Etiology/Pathogenesis

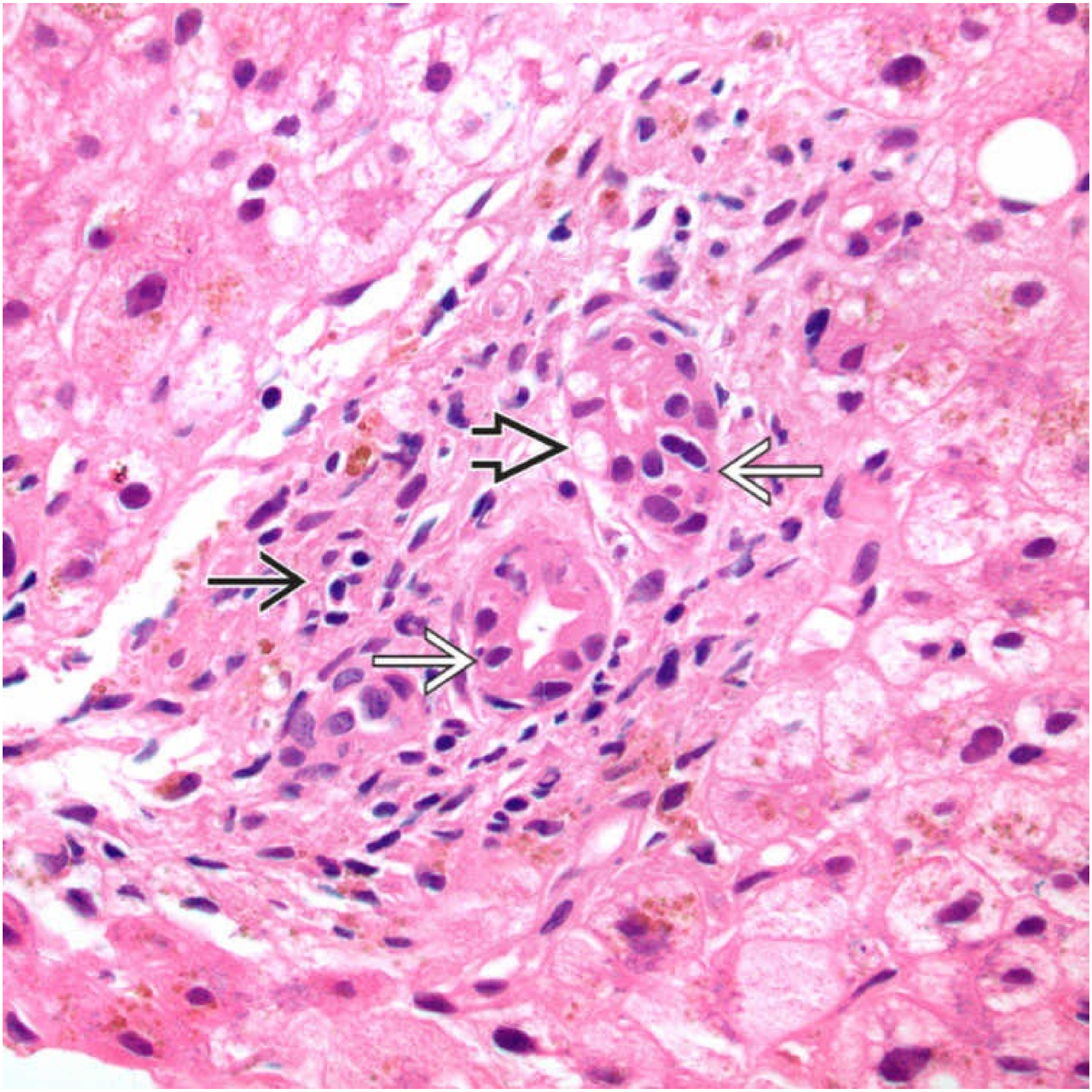
- Donor-derived T-lymphocyte response against immunocompromised host epithelium
  - Immunosuppressed recipient cannot destroy donor cells

Clinical Issues

- Represents major hepatic complication after stem cell transplant
- Common presenting signs are jaundice and hepatomegaly
- Elevated serum alkaline phosphatase and bilirubin
- Variably elevated transaminases

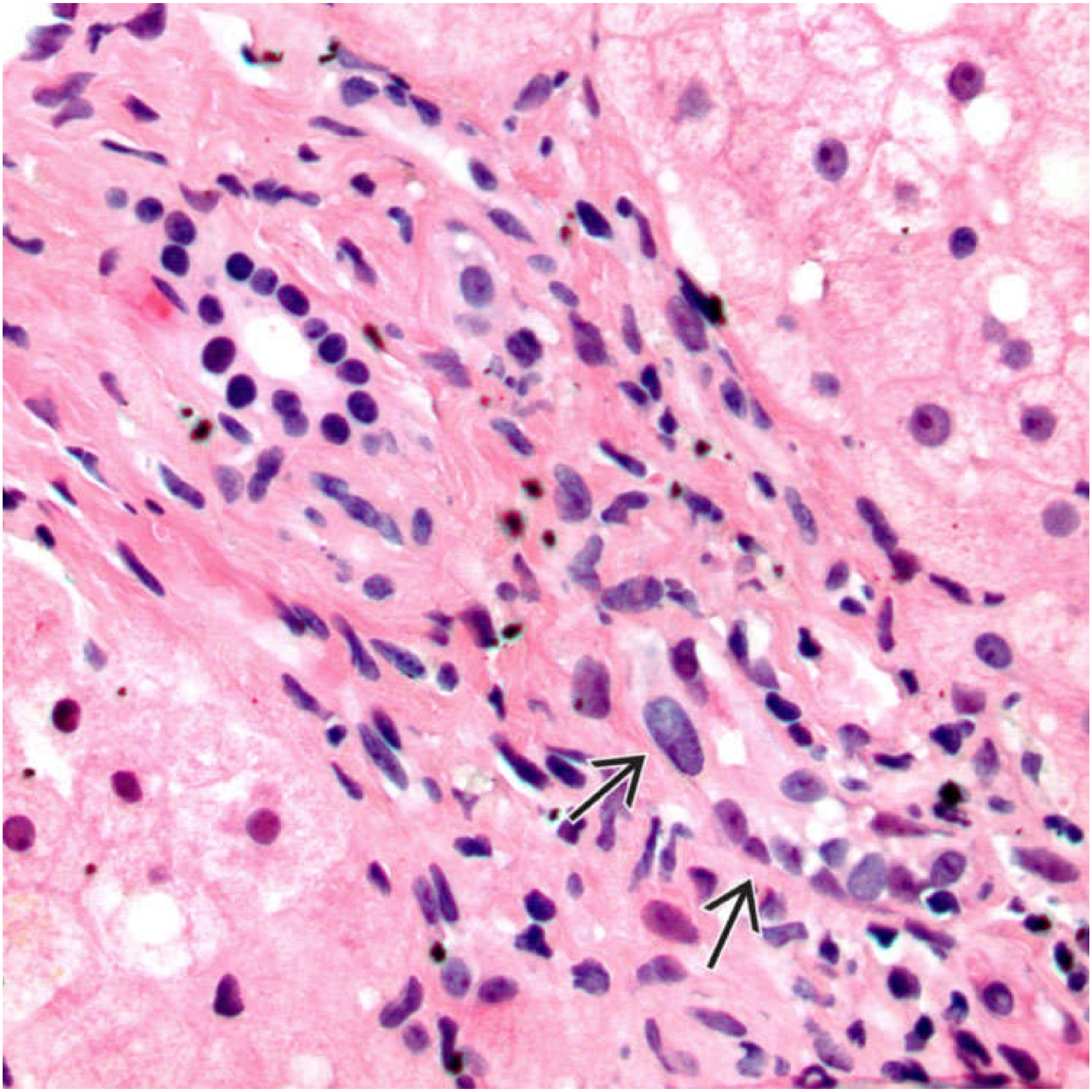
Microscopic

- Bile duct epithelial cell damage is key distinguishing feature
  - Epithelial cell vacuolization and attenuation
  - Withering, sloughing, and necrosis of biliary epithelial cells
  - Lymphocytic infiltration
  - Ductopenia with progression to chronic disease
- Portal inflammation is typically mild
- Endotheliitis in some cases
- Other nonspecific changes include cholestasis, lobular inflammation and hepatocyte swelling
- Acute hepatitis pattern also described
- Chronic graft-vs.-host disease features ductopenia, fibrosis
- Histologic findings may be focal

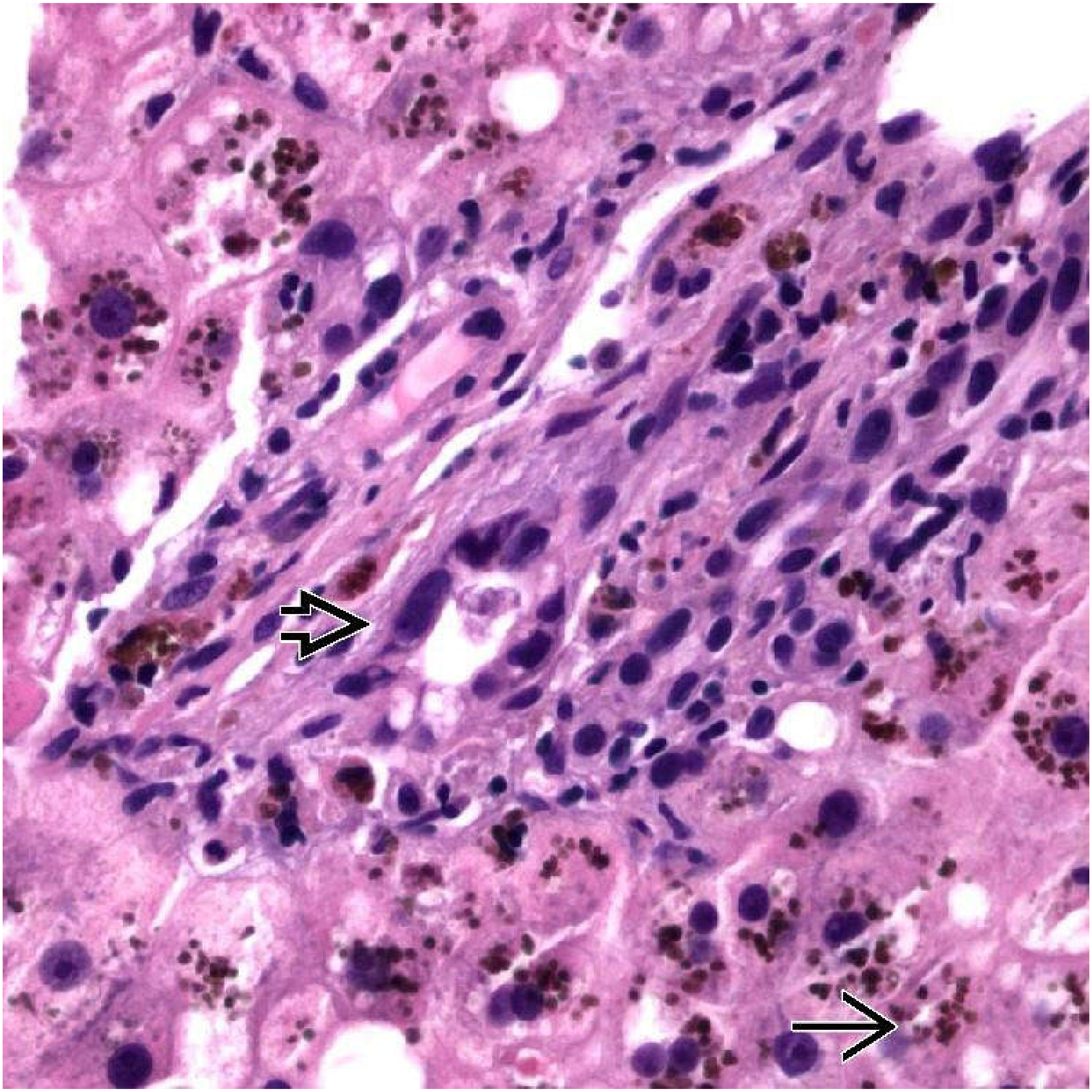


Bile Duct Injury in GVHD

Mild portal inflammation → and bile duct damage are seen in this case of hepatic graft-vs.-host disease (GVHD). The biliary epithelial cells are irregular and unevenly spaced ⇒ and show cytoplasmic vacuolization ⇨. The duct lumen is irregular as well. These are all features of biliary epithelial damage.

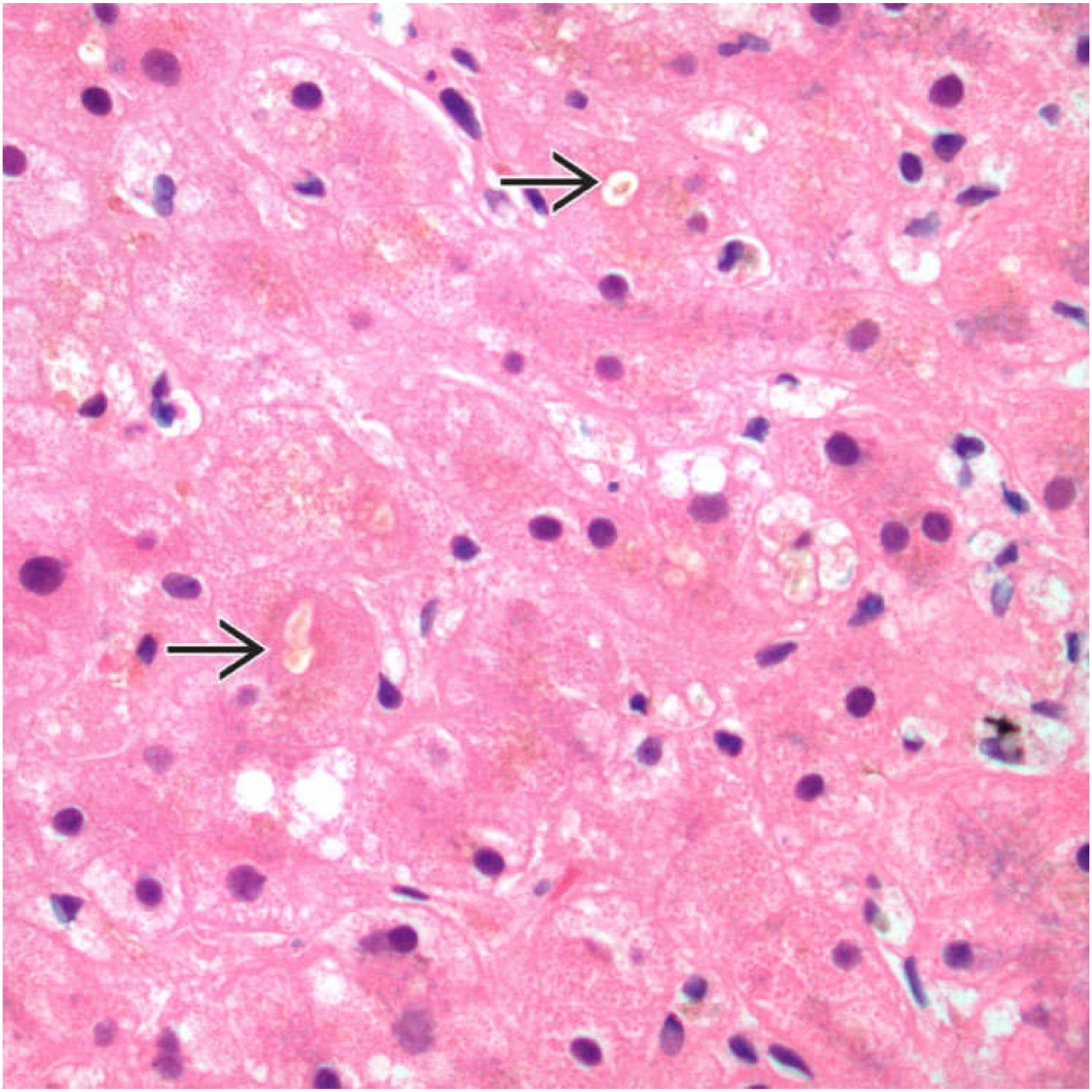


Bile Duct Epithelial Cell Injury
Bile duct epithelial cell nuclei are pleomorphic, varying in size and polarity, and unevenly spaced → in this case of GVHD. There is cytoplasmic vacuolization. The portal inflammation is mild.



Injured Bile Duct

This case of GVHD shows mild portal inflammation and biliary epithelial cell injury ⇨. The brown pigment indicates iron overload, which is often seen → in stem cell transplant recipients. The portal inflammation is mild.



Mild Cholestasis
H&E-stained slide shows nonspecific lobular changes seen in GVHD, including cholestasis →, mild inflammation, and hepatocyte swelling.

TERMINOLOGY

Abbreviations

- Graft-vs.-host disease (GVHD)

Synonyms

- "Vanishing bile duct syndrome" has been used as synonym, but is not specific term

- ○ Refers to loss of bile ducts in chronic GVHD, drug-related cholangitis, or allograft rejection

Definitions

- Attack of immunocompetent, donor-derived cells against recipient tissues
    - ○ Usually occurs in bone marrow transplant or hematopoietic stem cell transplant recipients
    - ○ Occurs infrequently after solid organ transplant and rarely after blood transfusion

ETIOLOGY/PATHOGENESIS

Immune-Mediated

- Donor-derived T-lymphocyte response against immunocompromised host epithelium
    - ○ Usually due to graft major histocompatibility complex incompatibility
    - ○ Immunosuppressed recipient cannot destroy donor cells
    - ○ Can also occur with autologous and syngeneic grafts

CLINICAL ISSUES

Epidemiology

- Incidence
    - ○ Represents major hepatic complication after stem cell transplant
    - ○ Affects most hematopoietic stem cell recipients at some point in their course

Presentation

- Jaundice
    - Hepatomegaly
    - Elevated liver function tests
    - ○ Elevated serum alkaline phosphatase and bilirubin
    - ○ Transaminases may also be elevated
    - ○ Transaminases can be markedly elevated in acute hepatitis pattern of GVHD
- Acute GVHD may also be accompanied by skin or GI tract involvement
    - ○ Rash, diarrhea, weight loss
- Chronic GVHD often presents with widespread disease
    - ○ Wasting disease with salivary gland, oral, ocular, and musculoskeletal involvement
- Hepatic failure and coagulopathy with advanced disease

Natural History

- Acute and chronic forms defined clinically but no clear dichotomy in liver histology
    - ○ Acute GVHD occurs < 100 days after transplant
    - ○ Chronic GVHD occurs > 100 days after transplant

Treatment

- Drugs
  - Increase immunosuppression
  - Corticosteroids are 1st-line therapy
  - Ursodeoxycholic acid used for prophylaxis

Prognosis

- Acute GVHD fatal in < 5% of patients
- Persistent jaundice is poor prognostic sign

MICROSCOPIC

Histologic Features

- Bile duct epithelial cell damage
  - Key feature that distinguishes GVHD from other forms of hepatic injury
    - Findings may be focal and not present in every portal tract
      - Damage of > 50% of ducts with minimal inflammation or duct loss (< 80% of portal tracts contain duct) is highly suggestive of GVHD
  - Lymphocytic infiltration of bile ducts
  - Epithelial cell vacuolization and attenuation
  - Withering, sloughing, and necrosis of biliary epithelial cells
  - Ductopenia with progression to chronic disease
- Endotheliitis may be seen but not present in all cases
- Other nonspecific changes
  - Portal inflammation, typically mild
  - Cholestasis
  - Hepatocyte swelling or apoptosis
  - Lobular inflammation
  - Fibrosis with progression to chronic disease
- Acute hepatitis pattern also described

DIFFERENTIAL DIAGNOSIS

Drug-Induced Liver Injury

- Wide variety of drugs cause bile duct damage/ductopenia
- Cause of elevated bilirubin but not usually biopsied
- Cyclosporine causes mild hyperbilirubinemia by inhibiting canalicular bile transport

Acute Hepatitis

• Acute hepatitis pattern of GVHD can mimic other causes of acute hepatitis

Primary Sclerosing Cholangitis

• Different clinical scenario, characteristic imaging help differentiate

Prolonged or Chronic Obstruction of Large Bile Ducts

• Imaging studies, clinical scenario help differentiate
• Prominent neutrophilic infiltrate, ductular reaction are not features of GVHD

SELECTED REFERENCES

1. Stift, J, et al. Consensus on the histopathological evaluation of liver biopsies from patients following allogeneic hematopoietic cell transplantation. *Virchows Arch*. 2014; 464(2):175–190.
2. McDonald, GB. Hepatobiliary complications of hematopoietic cell transplantation, 40 years on. *Hepatology*. 2010; 51(4):1450–1460.
3. Quaglia, A, et al. Histopathology of graft versus host disease of the liver. *Histopathology*. 2007; 50(6):727–738.

4. Shulman, HM, et al. Histopathologic diagnosis of chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: II. Pathology Working Group Report. *Biol Blood Marrow Transplant*. 2006; 12(1):31–47.

SECTION 9
TUMORS OF THE LIVER

OUTLINE

Hepatic Adenoma

KEY FACTS

Classification

- *HNF1A* mutated subtype
- β-catenin mutated subtype
- Inflammatory subtype
- Unclassified

Etiology/Pathogenesis

- Commonly associated with oral contraceptive or long-term steroid use
  - May regress after withdrawal of oral contraceptives
- Associated with obesity or ethanol use

Clinical Issues

- Typically in women of reproductive age
  - Noncirrhotic background liver
- Symptoms
  - Abdominal pain; acute, intermittent, or chronic
- Complications
  - Bleeding
  - Rupture; pregnancy is risk factor
  - Slight chance of malignant transformation

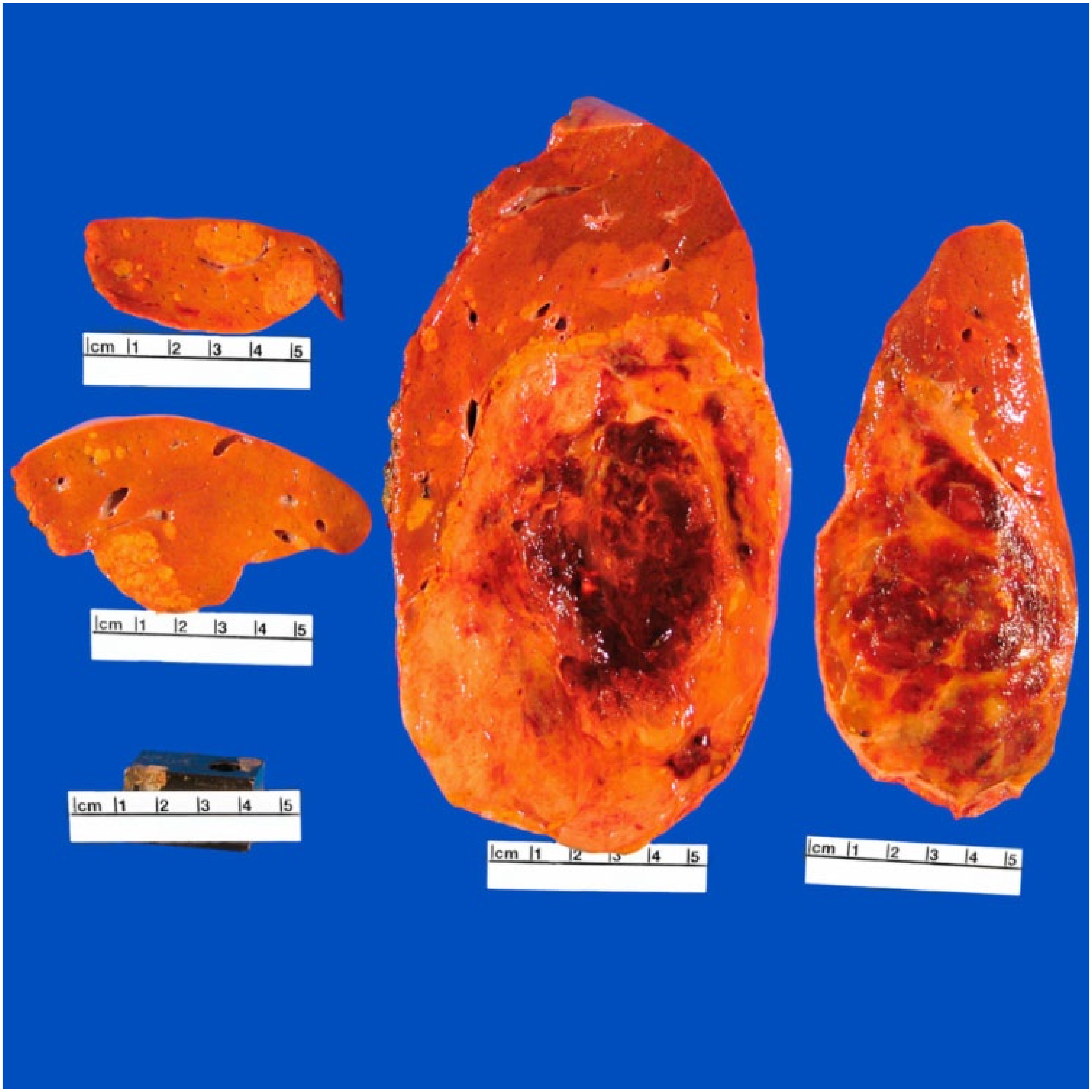
Microscopic

- Cords or sheets of benign hepatocytes with uniform nuclei
  - Low nuclear:cytoplasmic ratio
- Portal structures lacking
- Numerous unpaired arteries
- Intact reticulin framework
- Hemorrhage &/or infarcts may be present with hemosiderin-laden macrophages or fibrotic regions

Top Differential Diagnoses

- Well-differentiated hepatocellular carcinoma
- Focal nodular hyperplasia
- Nodular regenerative hyperplasia

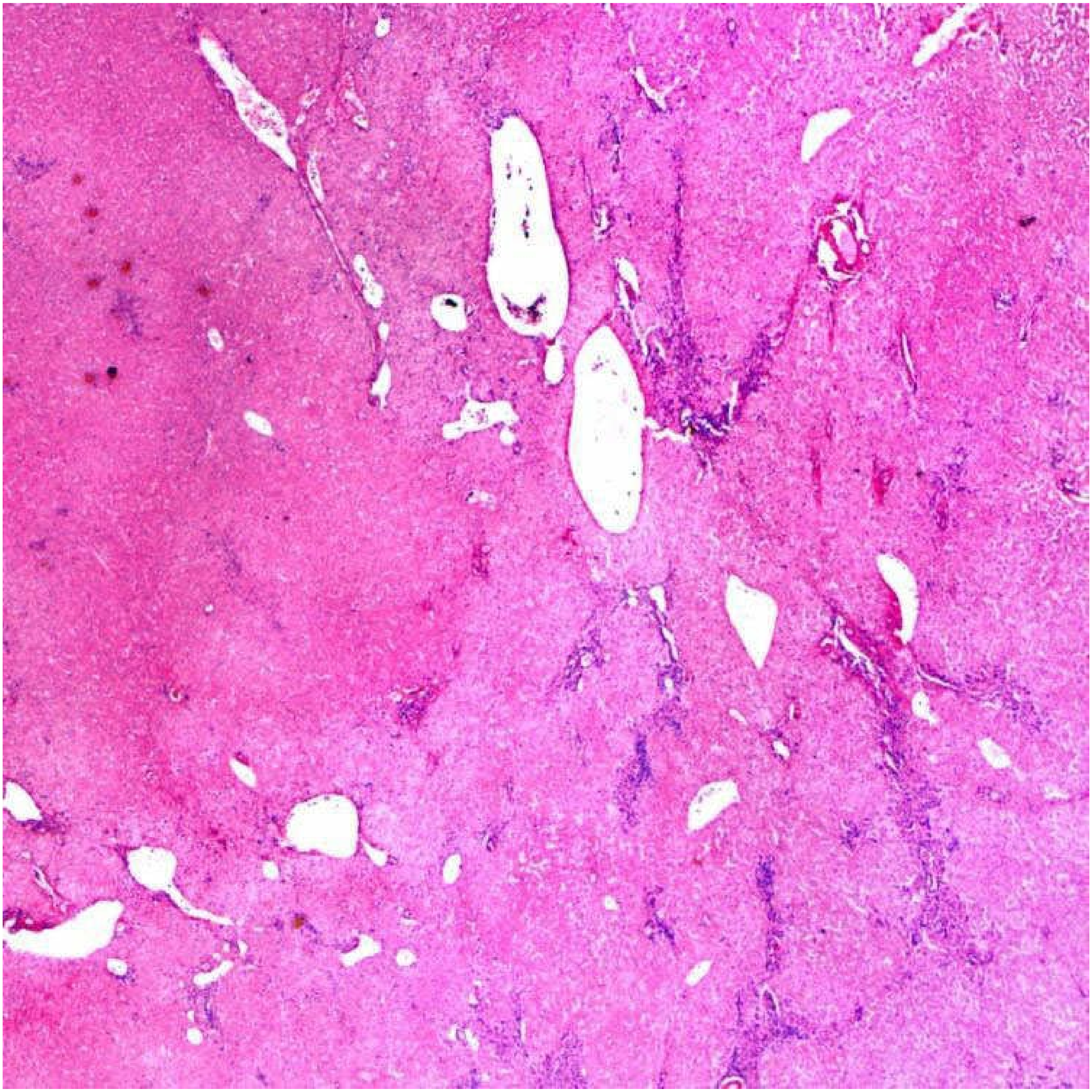
Gross Appearance
This large hepatic adenoma ⇨ is well demarcated and tan-brown with streaks of hemorrhage.



Hepatic Adenomatosis

This case of hepatic adenomatosis features multiple adenomas with hemorrhage and necrosis.

Gross Appearance
Areas of necrosis and hemorrhage are common in hepatic adenoma.



Sheets of Hepatocytes
Low-magnification view shows sheets of hepatocytes with numerous thin-walled vessels in hepatic adenoma.

TERMINOLOGY

Definitions

- Benign liver neoplasm composed of cells of hepatocytic origin
  - Adenomatosis
    - > 10 individual adenomas in 1 liver
    - Associated with
      - Glycogenosis type Ia or III

  - Klinefelter syndrome
  - Familial adenomatosis

ETIOLOGY/PATHOGENESIS

Definite Mechanism Unclear

- Sex hormones appear to play role
  - Commonly associated with oral contraceptive or long-term steroid use
  - Newer generation contraceptive pills with lower estrogen content may be associated with lower risk
- Also associated with obesity and ethanol use
- Also associated with glycogen storage disease types I and III, galactosemia, tyrosinemia

CLINICAL ISSUES

Epidemiology

- Age
  - Reproductive age in women
- Sex
  - Typically women

Presentation

- Liver mass
  - Arising in noncirrhotic liver without underlying liver disease
  - May be multiple
- Symptoms
  - Abdominal pain
    - Acute, intermittent, or chronic
- May be asymptomatic; found on imaging (20% of cases)
- Associated clinical conditions
  - Oral contraceptive use
    - May regress after withdrawal of oral contraceptives
  - Obesity
  - Metabolic syndrome
  - Excessive alcohol use
  - Anabolic steroid use
  - Tobacco use
  - Glycogen storage disease
  - Maturity-onset diabetes of young (MODY) type 3

Laboratory Tests

- Serum liver tests usually normal including α-fetoprotein

Treatment

- Stop oral contraceptives
  - Locoregional therapies
  - Surgical resection
  - If tumors exceeds 5 cm
  - If growing in fear of
    - Bleeding
    - Rupture
    - Malignant transformation
- Liver transplantation in some cases (multiple, etc.)

Prognosis

- Complete surgical resection should be curative
  - Rarely, malignant transformation (4-10%), bleeding, or rupture
  - Prevalence of malignancy 10x higher in affected men compared to female counterpart

MACROSCOPIC

General Features

- Unencapsulated, well-demarcated, solitary or multiple masses
- Tan-brown, may have hemorrhage or necrosis

Size

- 1-30 cm

MICROSCOPIC

Histologic Features

- Background of noncirrhotic liver
  - Cords or sheets of benign hepatocytes
  - Low nuclear:cytoplasmic ratio
  - Regular and uniform nuclei, lack prominent nucleoli
  - Mitoses rare
  - Fat and glycogen may be abundant in tumor cells
  - Pseudoacinar or pseudoglandular structures typically lacking
- Architectural features
  - Portal structures lacking
  - Increased unpaired arteries
  - Compressed sinusoidal spaces
  - Bile ducts absent, but ductules may be present
  - Intact reticulin framework

- Hemorrhage &/or infarcts may be present
  - With hemosiderin-laden macrophages or fibrotic regions
- Subtype
  - *HNF1A* mutated subtype
    - About 35%
    - Loss of liver fatty acid binding protein (LFABP-1) staining in tumor
    - Fat in tumor is common
    - Associated with oral contraceptive use in women
    - Do not occur in patients with glycogen storage disease
    - Lowest rate of malignant transformation among all subtypes
      - Clinical surveillance warrantable in small tumors
  - β-catenin mutated subtype
    - ~ 15%
    - Activation of β-catenin by mutations in exon 3
      - 1/2 displayed both inflammatory and β-catenin-activated phenotypes
    - Risk of malignant transformation caused by IL6ST somatic mutation activating gp130 in 60% of cases
    - Diffuse immunohistochemical staining pattern of glutamine synthetase
    - Positive β-catenin nuclear staining
    - Clinical and histologic features overlapped with hepatocellular carcinoma (HCC)
      - Male
      - Cytologic atypia
      - Pseudoacinar architecture
      - Diffuse glutamine synthetase staining pattern
      - Positive β-catenin nuclear staining
  - Inflammatory subtype
    - ~ 50%
      - Caused by IL6ST mutation in 60% of cases
      - Other may be mutated for STAT3 or GNAS
    - Prominent sinusoidal dilatation (telangiectasia) within tumor
    - Presence of bile ductules and inflammation
    - Background of fatty liver is common
    - Positive serum amyloid A &/or CRP stainings
      - Higher specificity but lower sensitivity of serum amyloid A compared to C-reactive protein staining
    - 10% have β-catenin activated mutation
  - Unclassified
    - 10%
    - Neither Wnt/β-catenin nor JAK/STAT-activated
    - Cannot be classified into any of above subtypes
    - No HNF1α inactivation
- LFABP, serum amyloid (SAA), C-reactive protein (CRP) cannot be used to distinguish from HCC because loss of LFABP and expression of SAA and CRP can be seen in HCC
- Combined use of HSP 70 and glutamine synthetase useful in distinction of hepatocellular adenoma from atypical hepatocellular neoplasms and well-differentiated HCC

DIFFERENTIAL DIAGNOSIS

Well-Differentiated Hepatocellular Carcinoma

- Cytologic atypia with increased nuclear:cytoplasmic ratio and prominent nucleoli
  - Thickened trabecula and pseudoglandular formation
  - Reticulin and immunohistochemical stains may help
  - Reticulin: Loss of reticulin suggests hepatocellular carcinoma, but reticulin may be lost in fatty area of hepatocellular adenoma
  - Positive glypican-3 (cytoplasmic) staining supports hepatocellular carcinoma
  - β-catenin: Positive (nuclear) staining supports hepatocellular carcinoma
  - Glutamine synthase: Extensive staining of hepatocytes in all zones supports hepatocellular carcinoma
- Often arises in background of cirrhosis &/or chronic liver disease
- More common in men and older individuals of either sex

Focal Nodular Hyperplasia

- Thick, fibrous septa containing thick-walled arteries at periphery
- Prominent bile ductular reaction and inflammatory infiltrate in fibrous septa
- Immunohistochemical stain for glutamine synthetase shows map-like staining pattern in FNH

Nodular Regenerative Hyperplasia

- Diffuse nodular appearance throughout liver without cirrhosis

Metastatic Carcinoma

- History of primary carcinoma elsewhere
- Usually negative for Hep-Par1or arginase-1 immunohistochemical stain

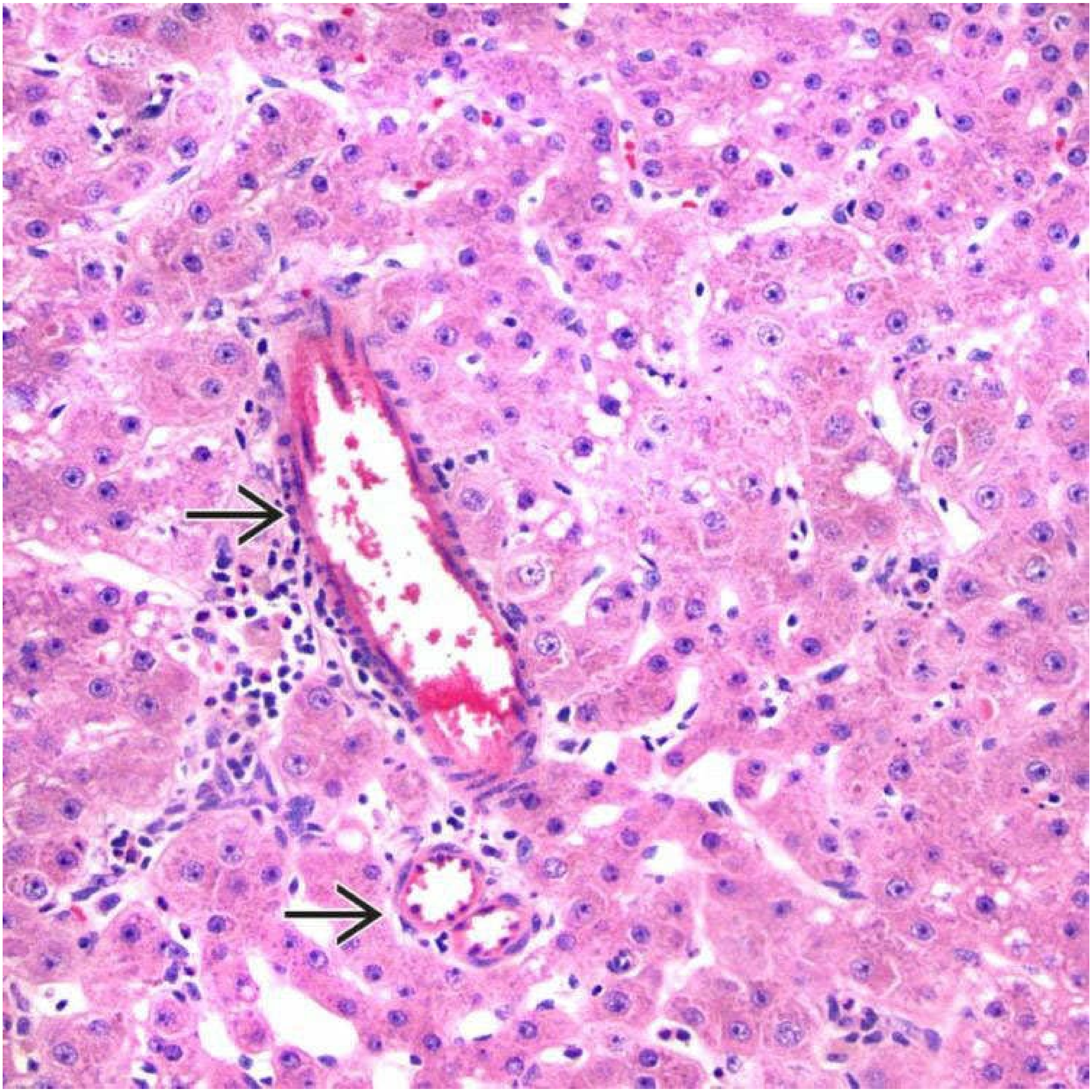
Atypical Hepatocellular Neoplasm

- Hepatocellular adenoma with atypical features
  - Arising in men
  - Older women
  - Focal atypical morphological features

DIAGNOSTIC CHECKLIST

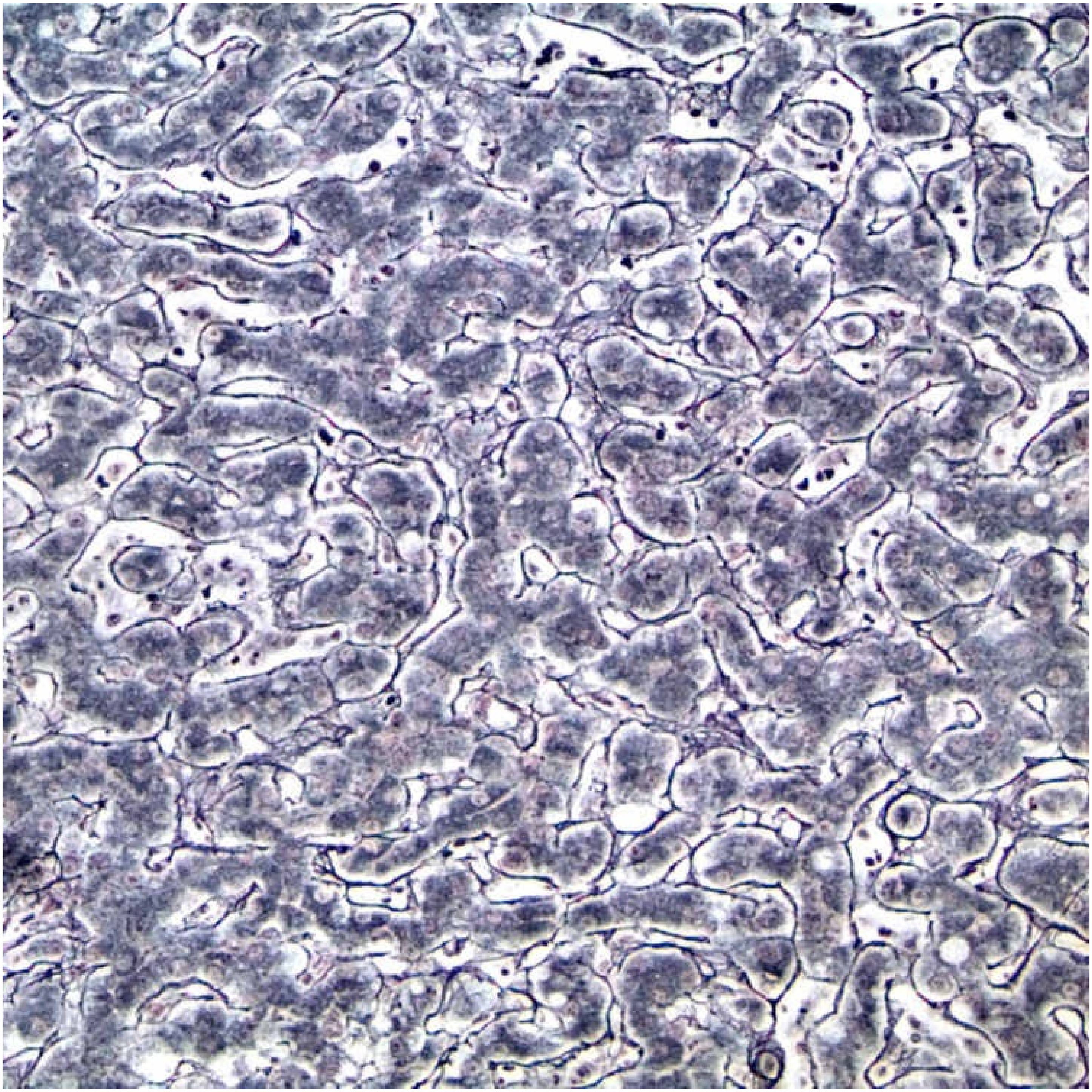
Clinically Relevant Pathologic Features

- Liver mass in individuals on long-term oral contraceptives/steroids
- Individuals on long-term anabolic steroids
- Be very cautious when making this diagnosis in men

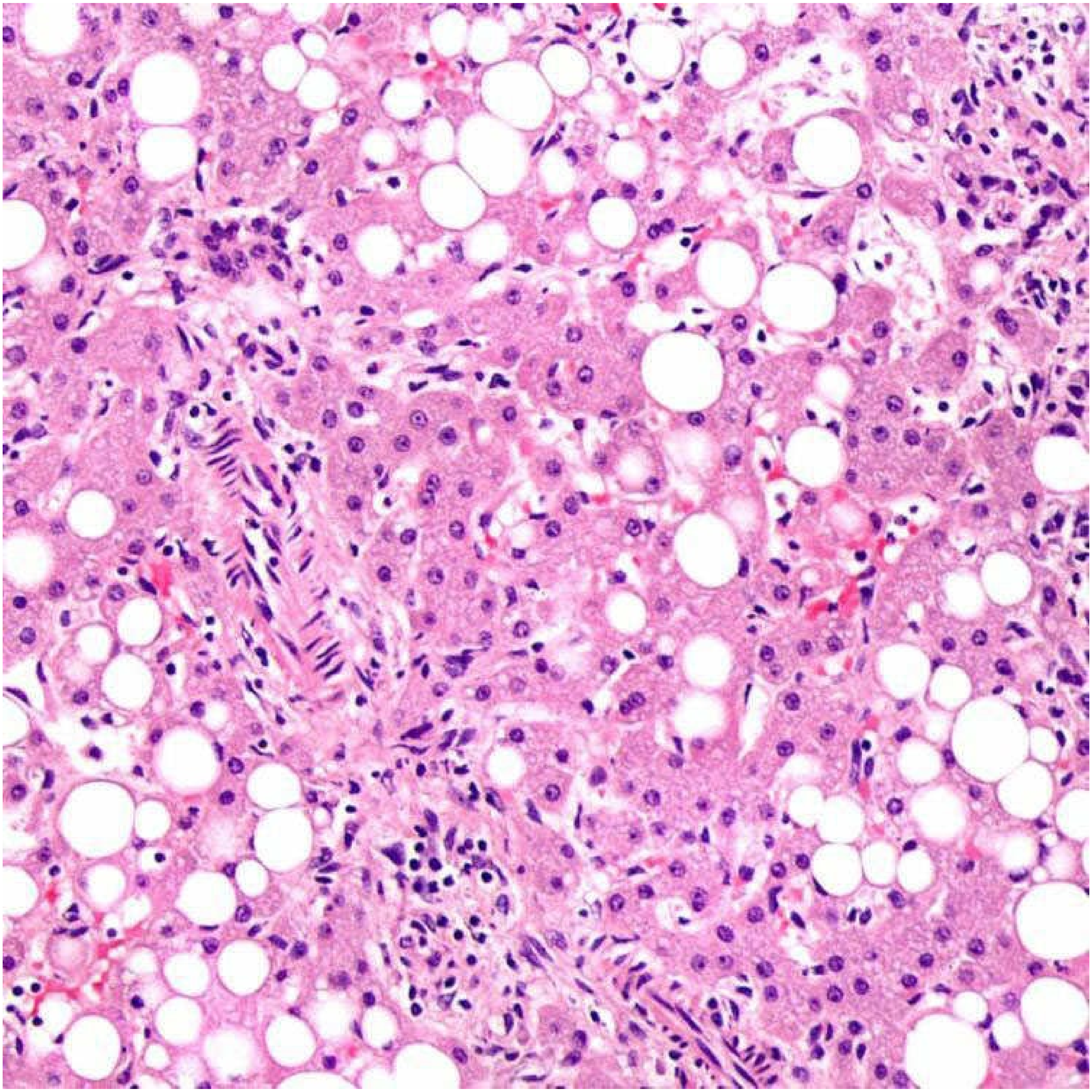


Benign Hepatocytes

Hepatic adenoma is shown with benign hepatocytes arranged in thin trabeculae and unpaired arteries → .



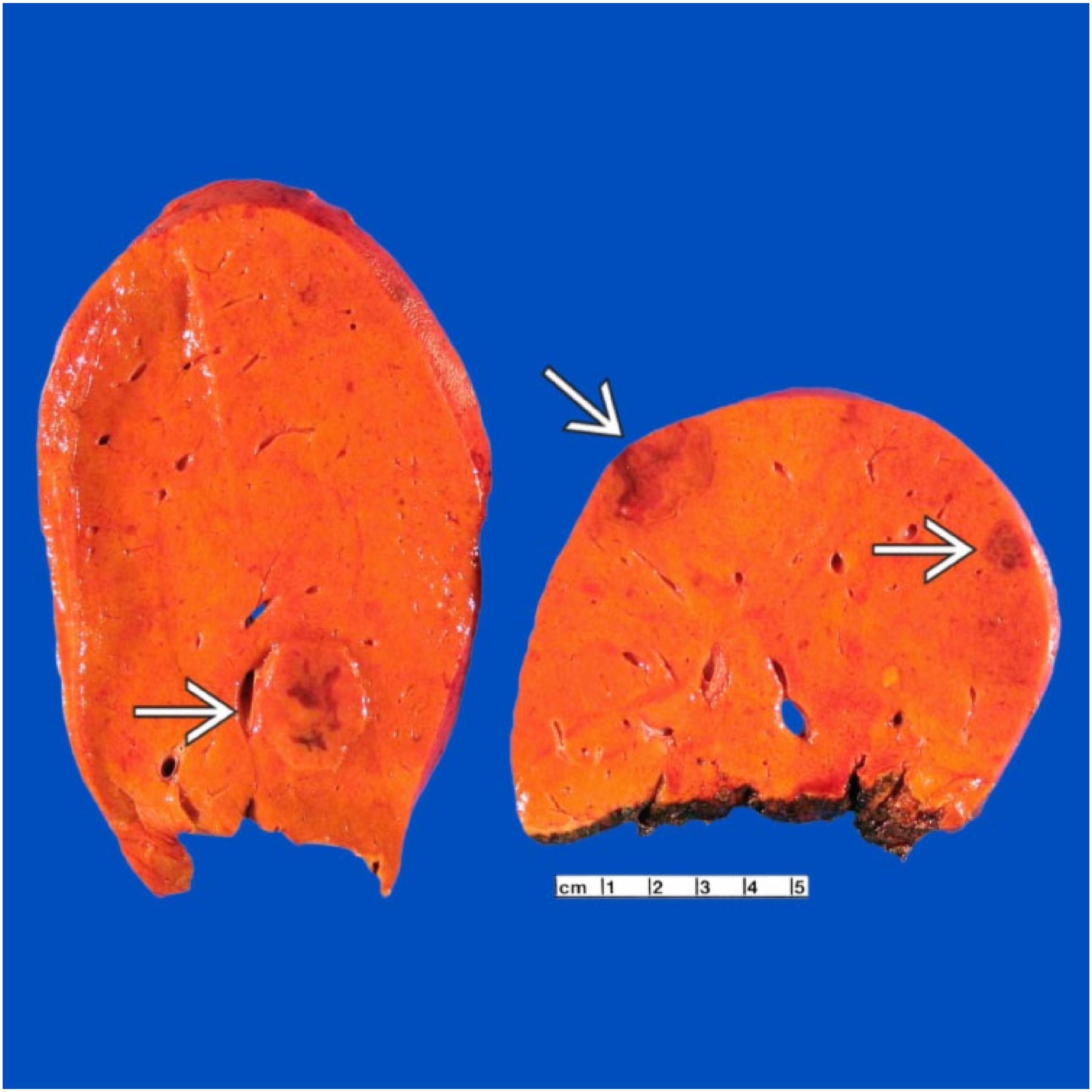
Normal Reticulin Framework
Hepatic adenomas have an intact, normal reticulin framework without thickened trabeculae or loss of reticulin.



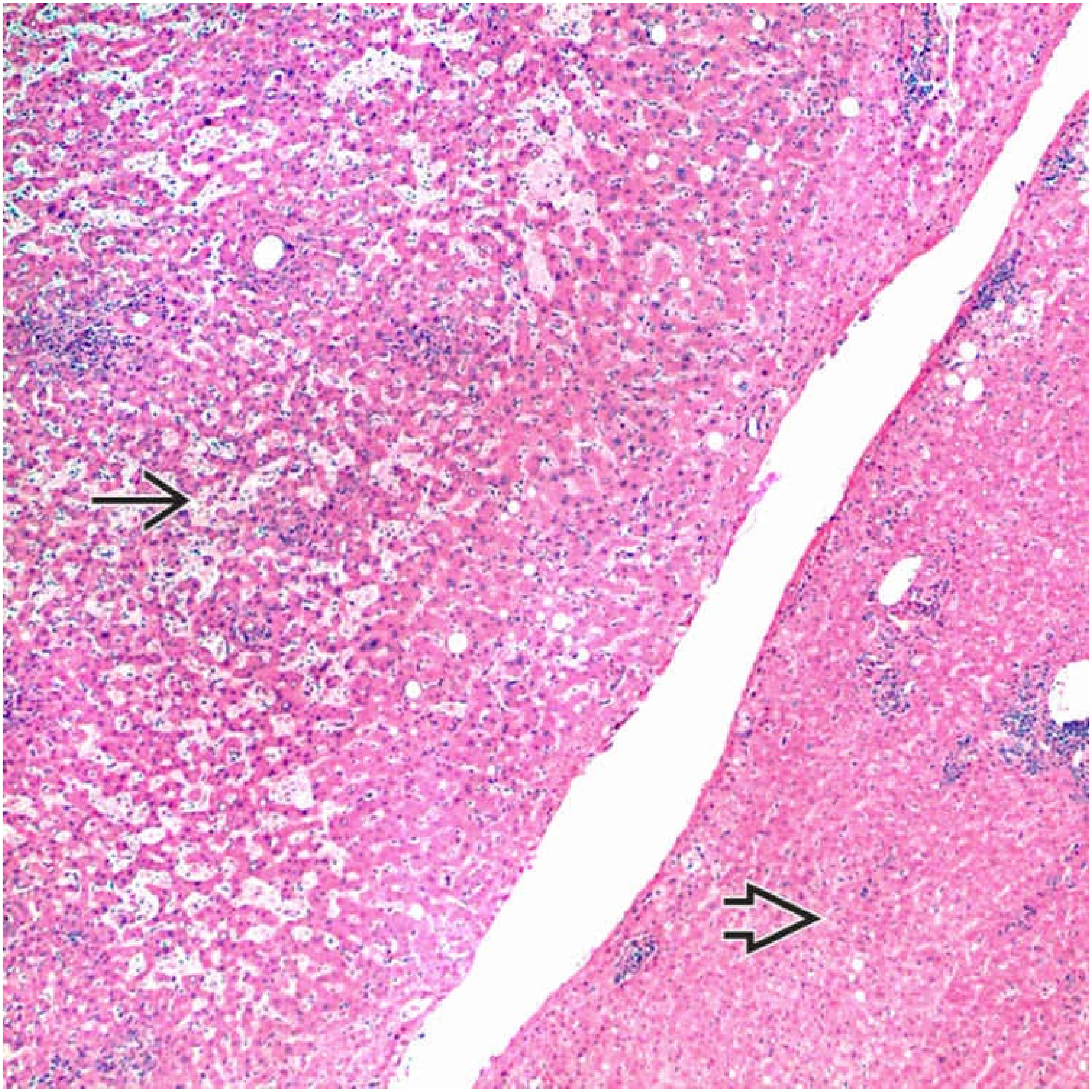
Fatty Change
High-power view of adenoma illustrates that fatty change is a common finding.

LFABP-1 Stain

Immunohistochemistry for LFABP-1 shows negative staining within the hepatic adenoma but retained staining in the nontumor liver in hepatic adenoma, HNF1A subtype.

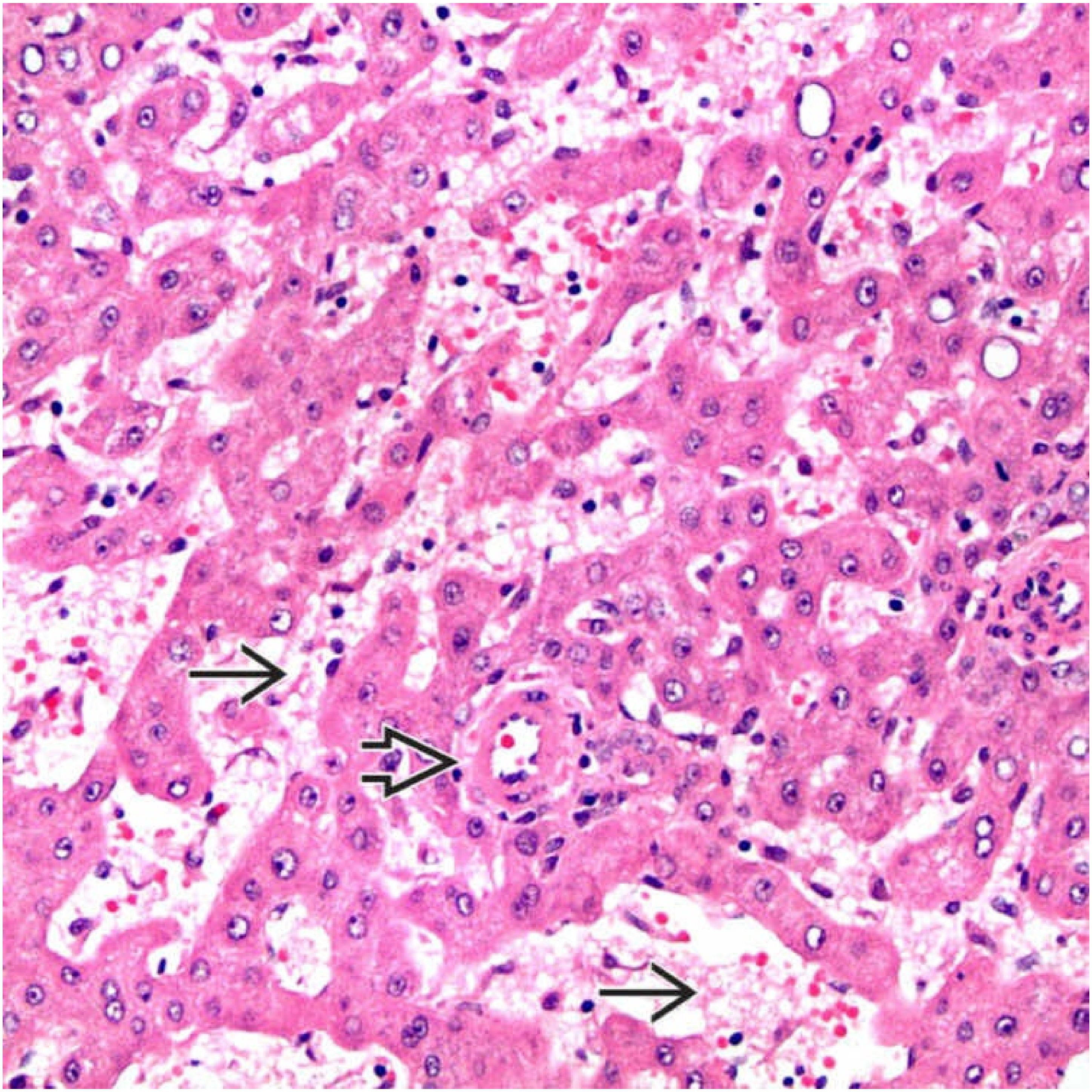


Gross Appearance
Gross photo shows multiple hepatic adenomas ⇒ .



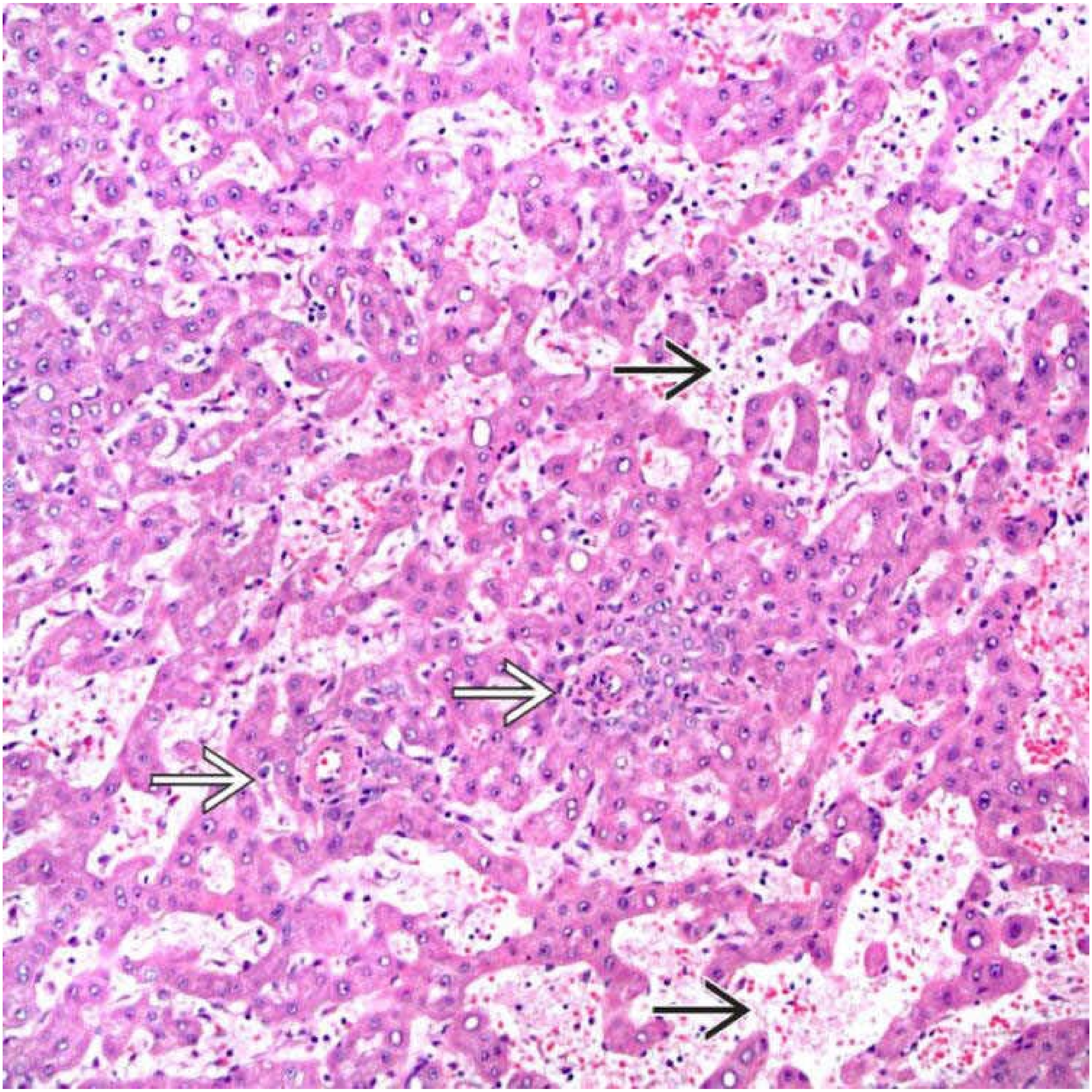
Telangiectatic Features

Low-magnification view shows telangiectatic features of hepatic adenoma, inflammatory subtype → on the left, with prominent dilated sinusoids, and nonneoplastic liver ⇨ on the right.



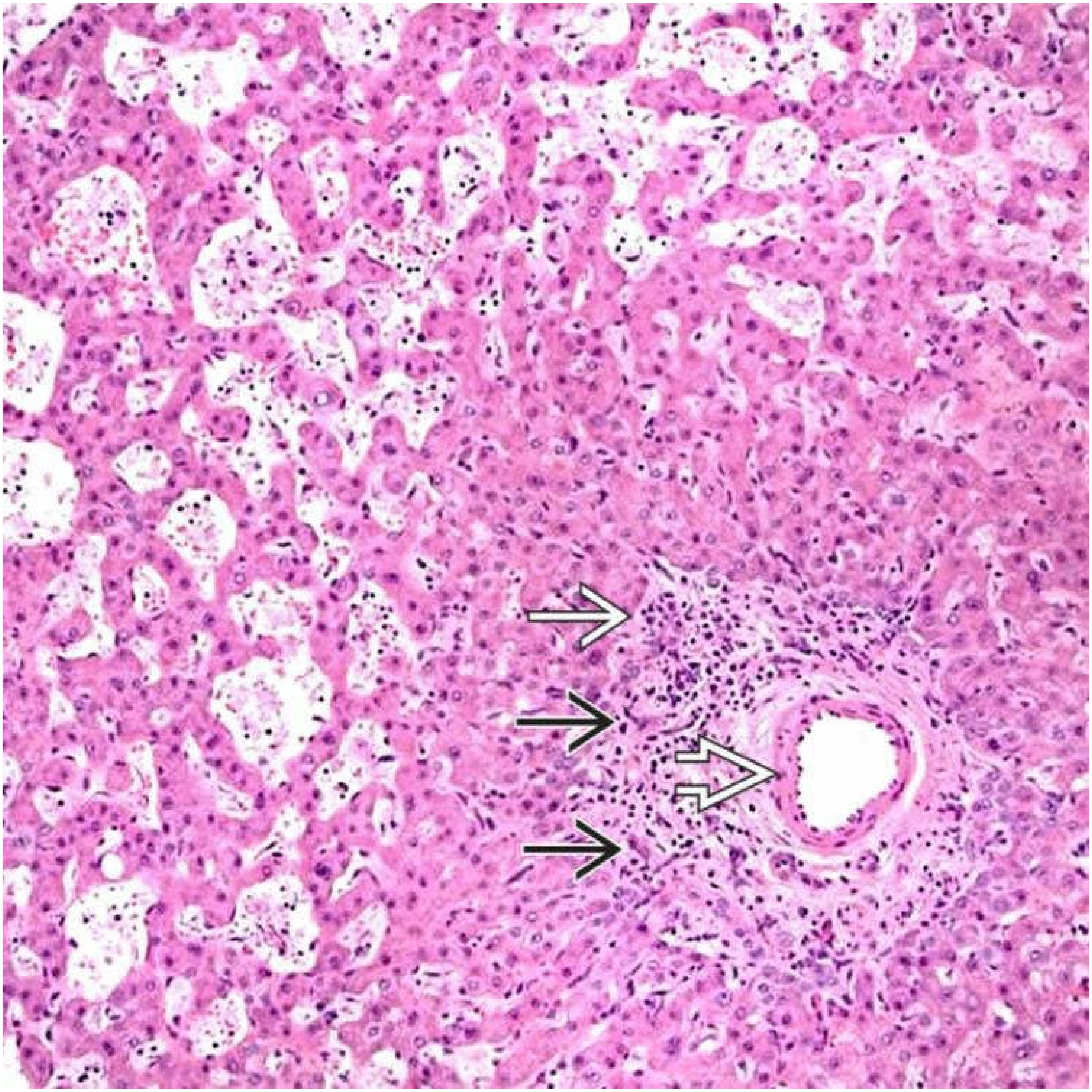
Hepatocellular Adenoma, Inflammatory Subtype

Dilated sinusoids → and an unpaired artery ⇨ are seen in this hepatic adenoma, inflammatory subtype.

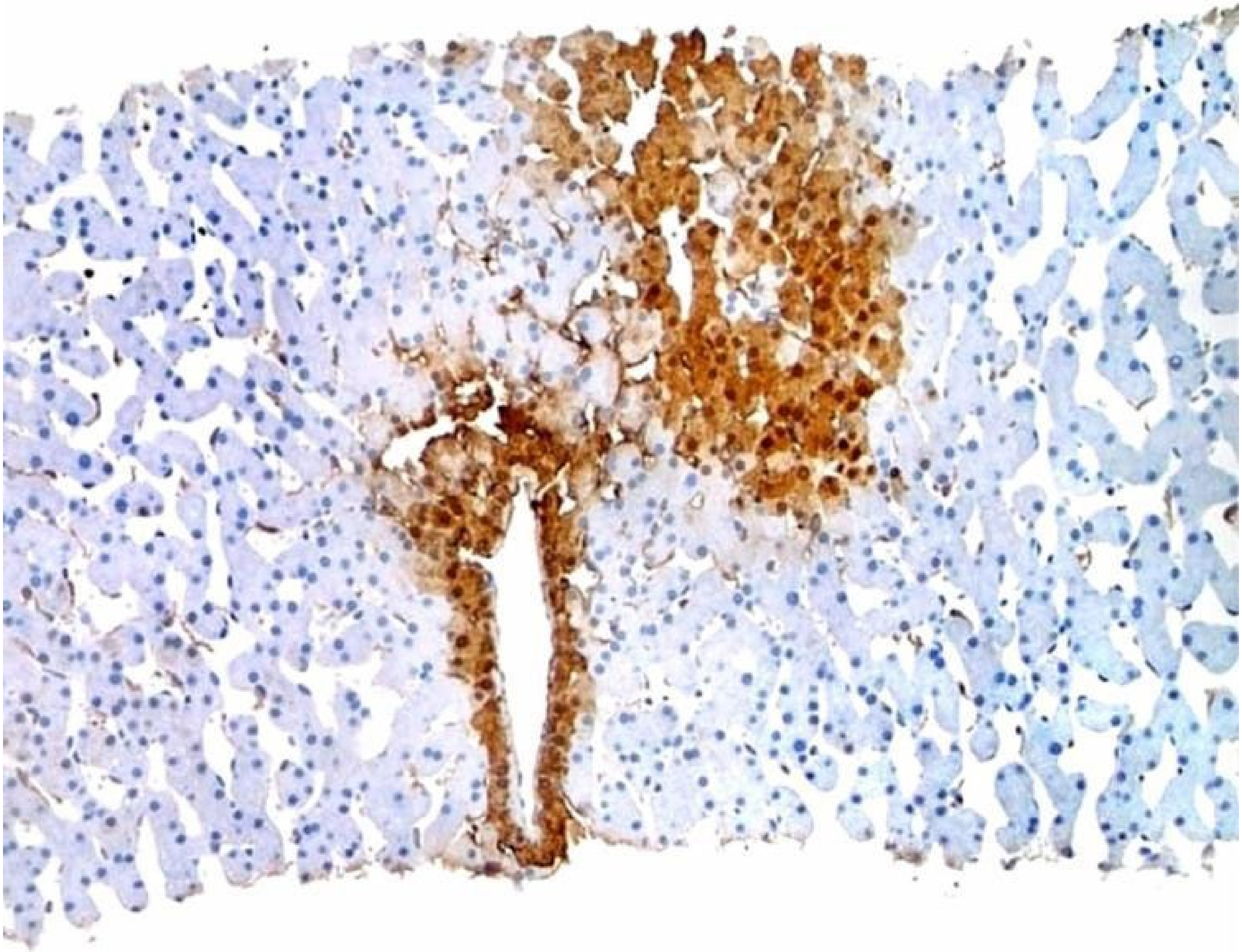


Hepatocellular Adenoma, Inflammatory Subtype

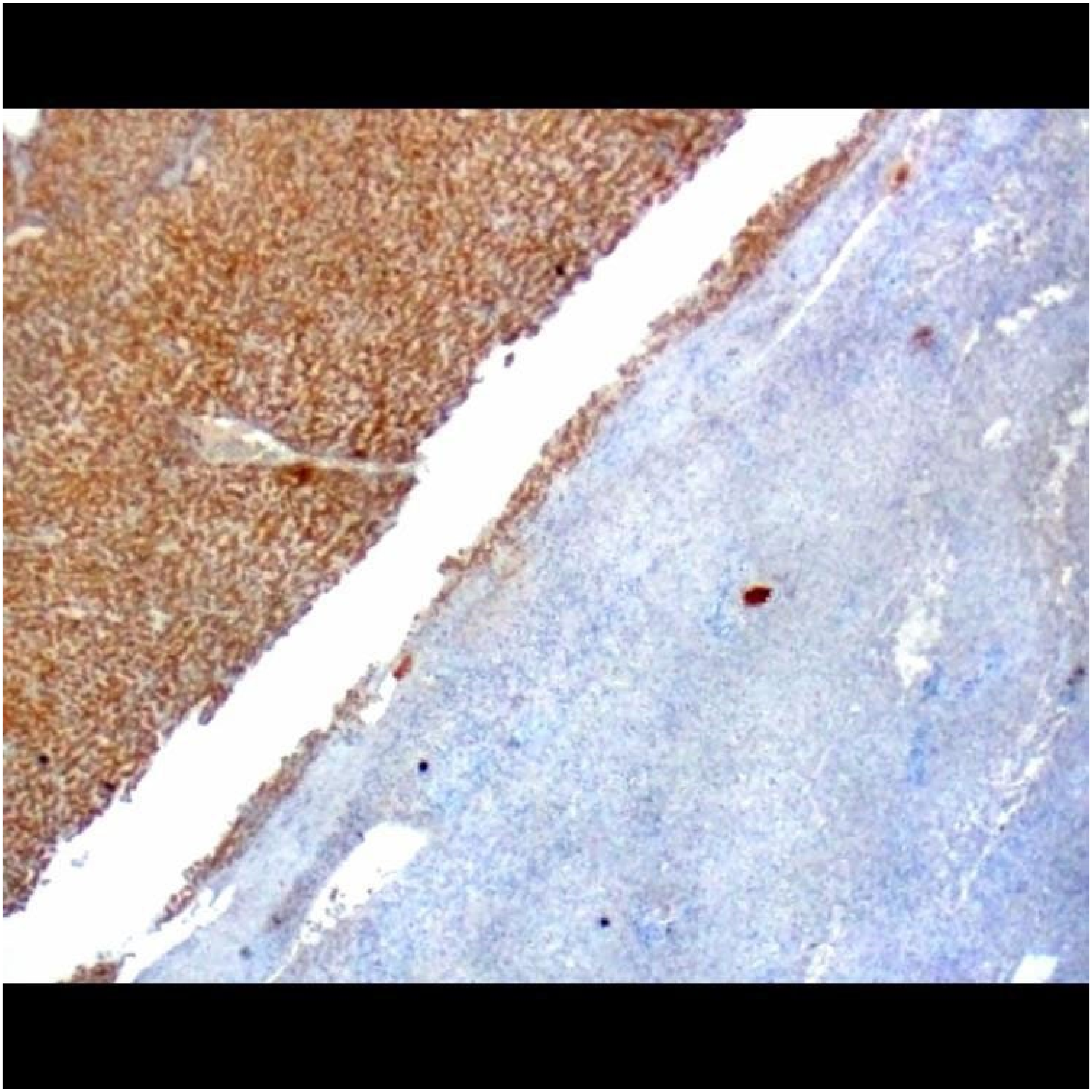
Dilated sinusoids → and unpaired arteries ⇒ are seen in this hepatic adenoma, inflammatory subtype.



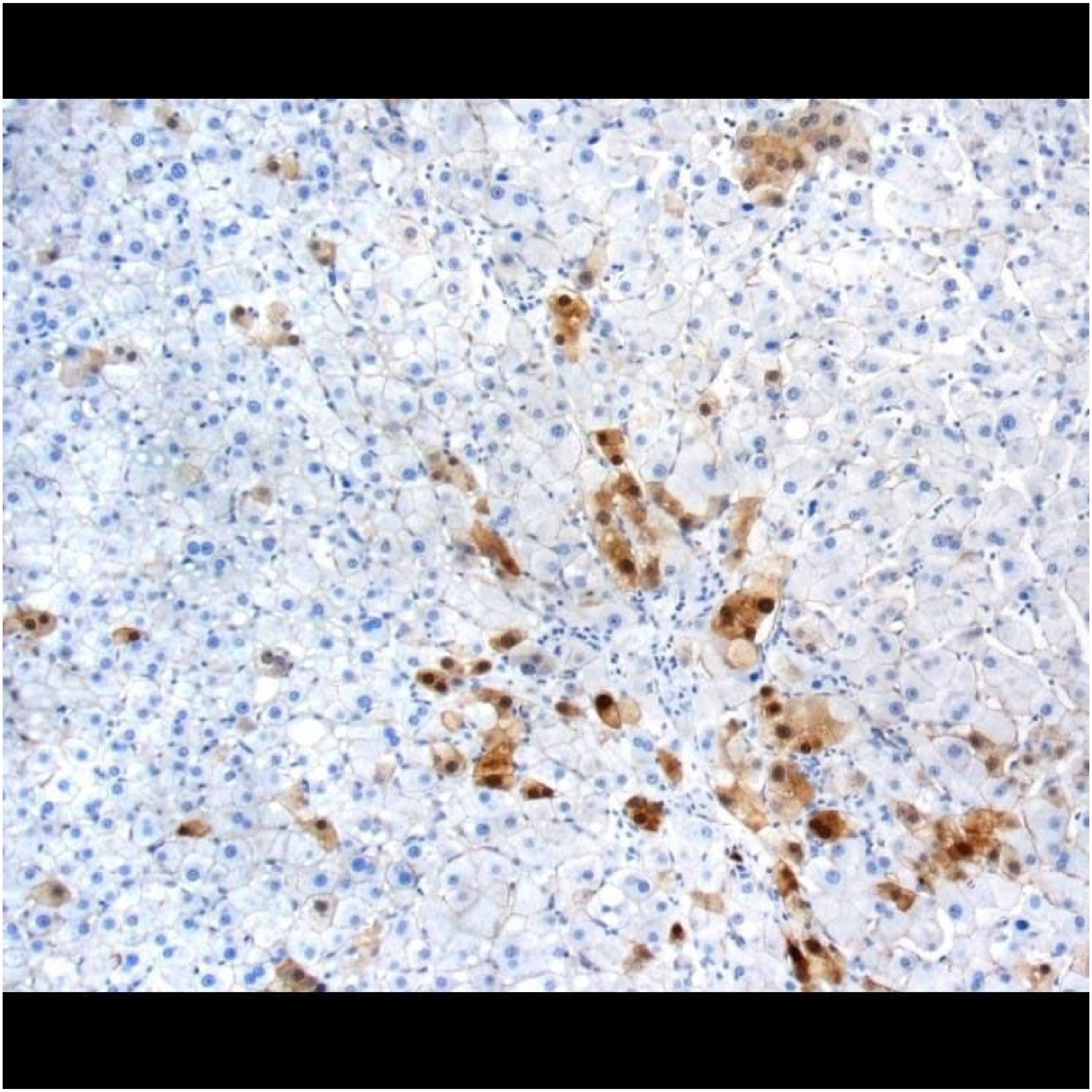
Hepatocellular Adenoma, Inflammatory Subtype
Unpaired artery ⇨, inflammation ⇒, and bile ductules → are shown in hepatic adenoma, inflammatory (telangiectatic) subtype, which may mimic focal nodular hyperplasia.



Glutamine Synthase
Immunohistochemistry for glutamine synthase shows the normal perivenular staining in hepatic adenoma.

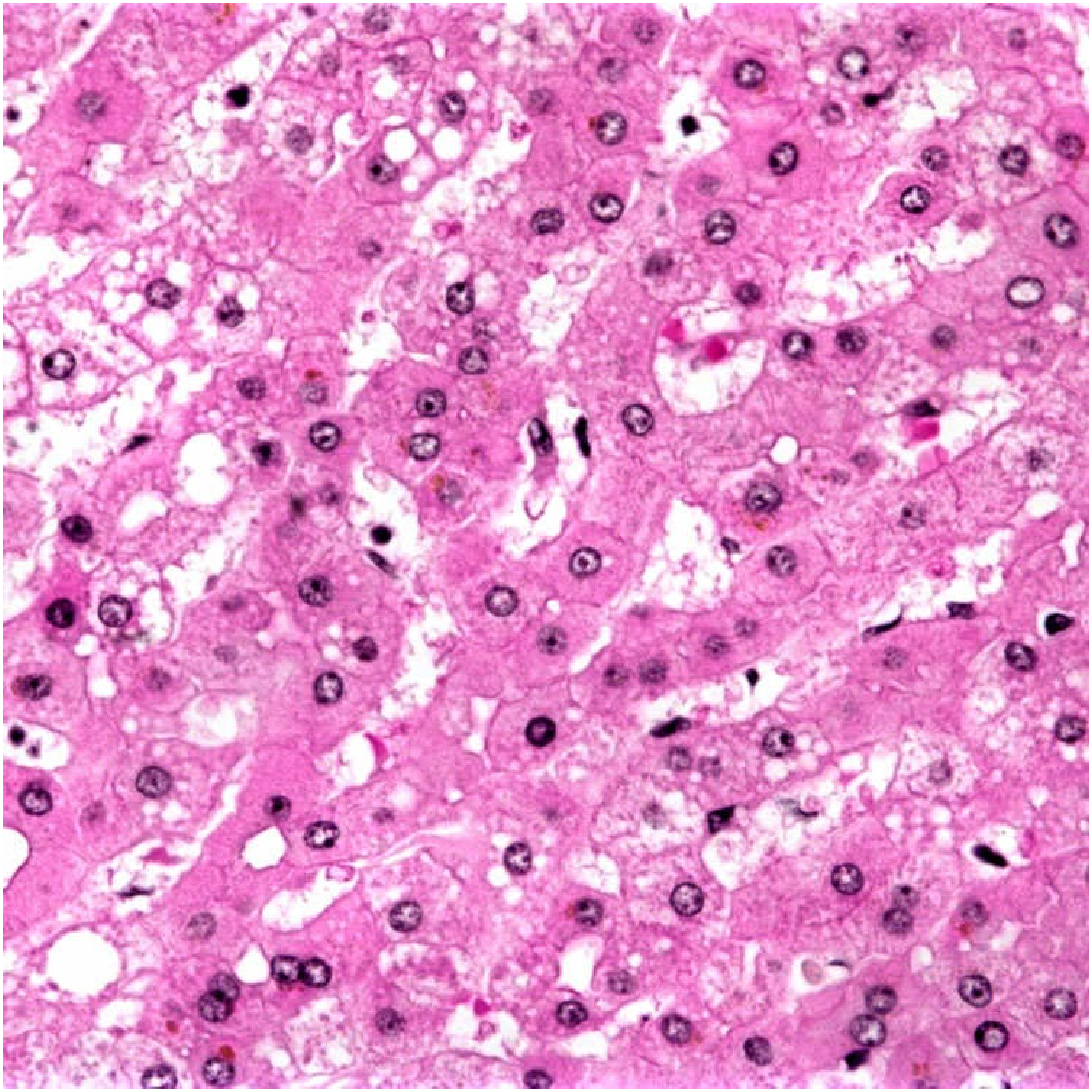


C-Reactive Protein in Hepatocellular Adenoma, Inflammatory Subtype
Diffuse staining for CRP (C-reactive protein) in the hepatocellular adenoma, inflammatory subtype is shown.



β-Catenin-Mutated Subtype β

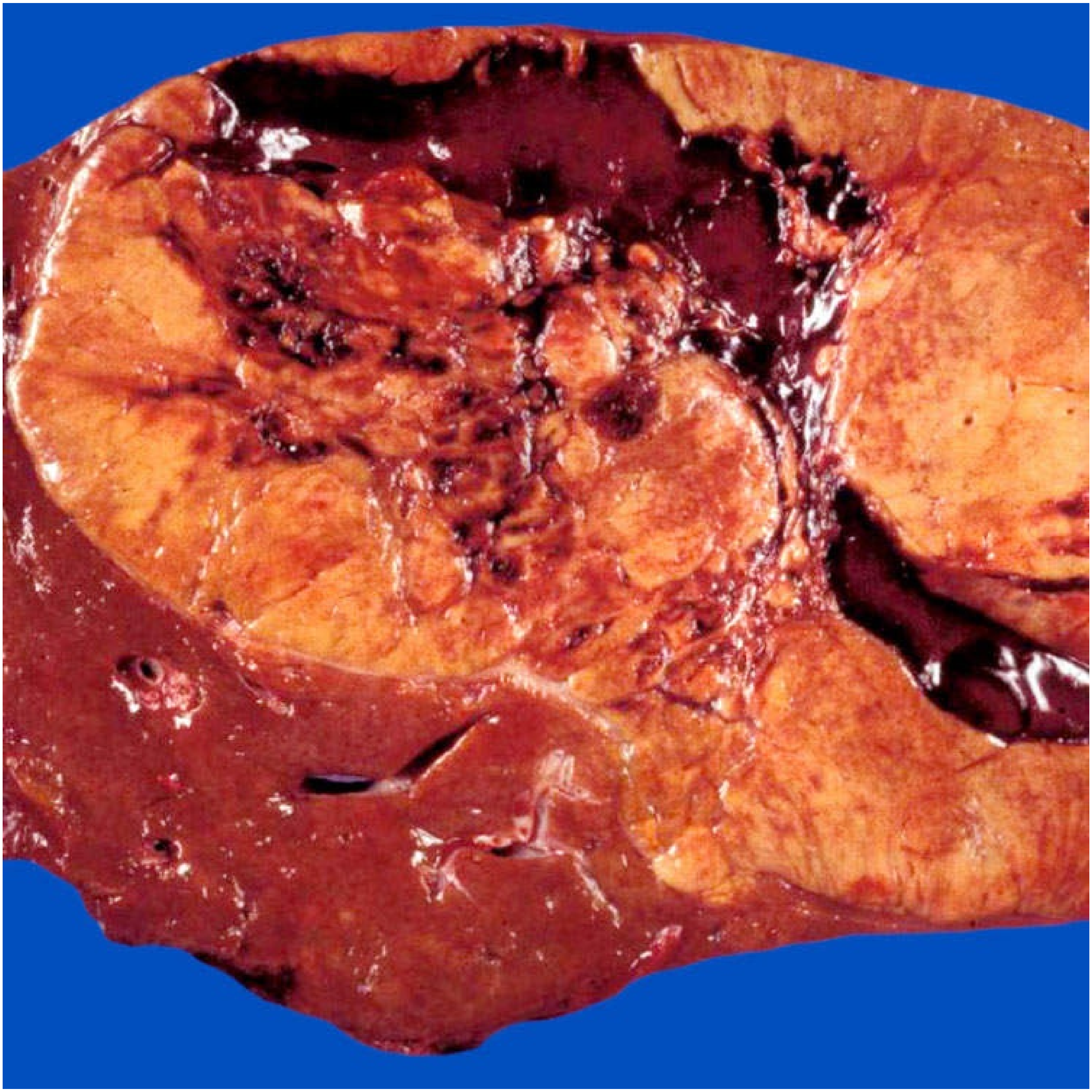
Positive nuclear staining for β-catenin is shown in hepatic adenoma, β-catenin-mutated subtype.



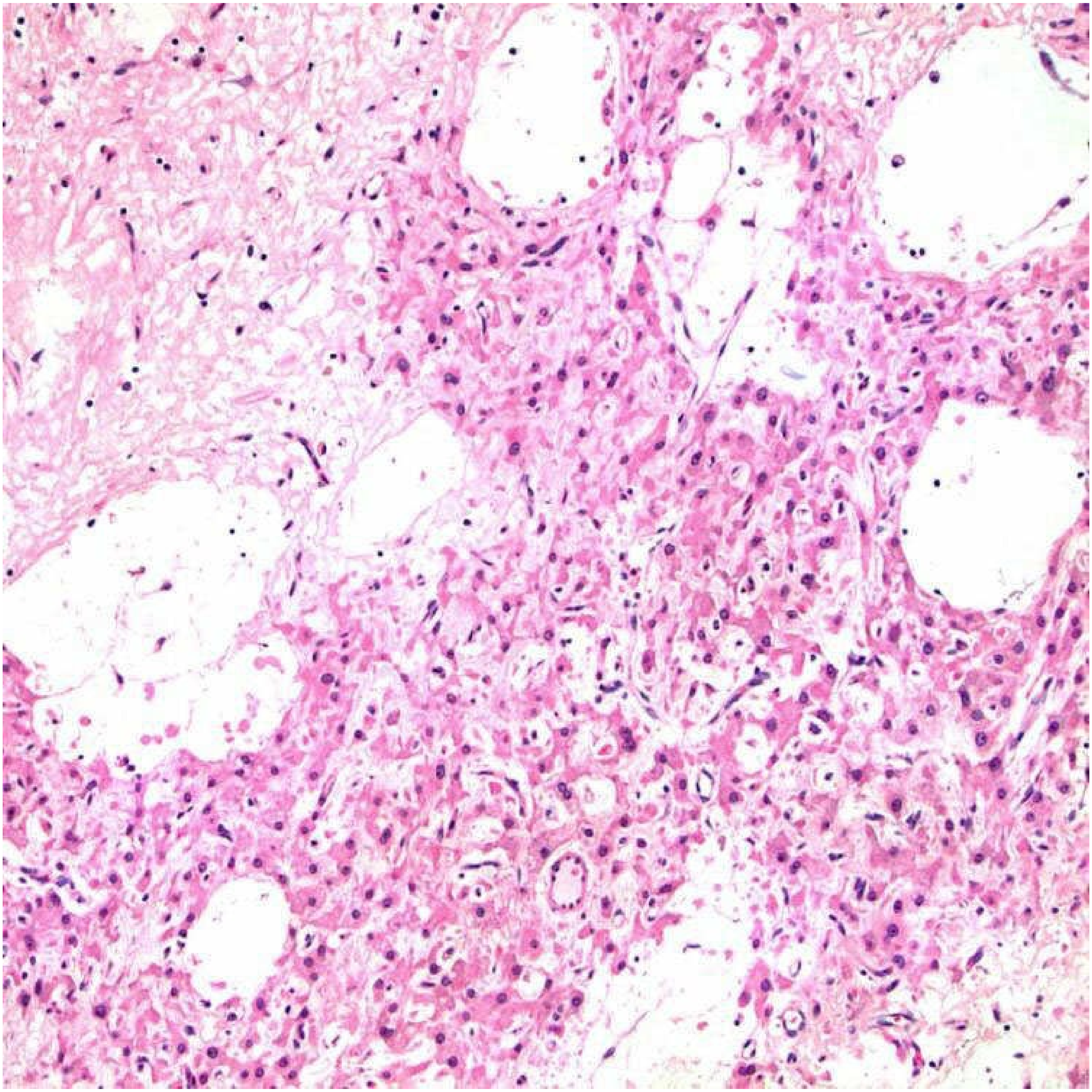
Neoplastic Hepatocytes
High-power view of the neoplastic hepatocytes in hepatocellular adenoma illustrates their uniformity and low N:C ratio.

Gross Appearance
Partial hepatectomy specimen shows a well-circumscribed, yellow-tan, hepatocellular adenoma under the capsule in a background of noncirrhotic liver.

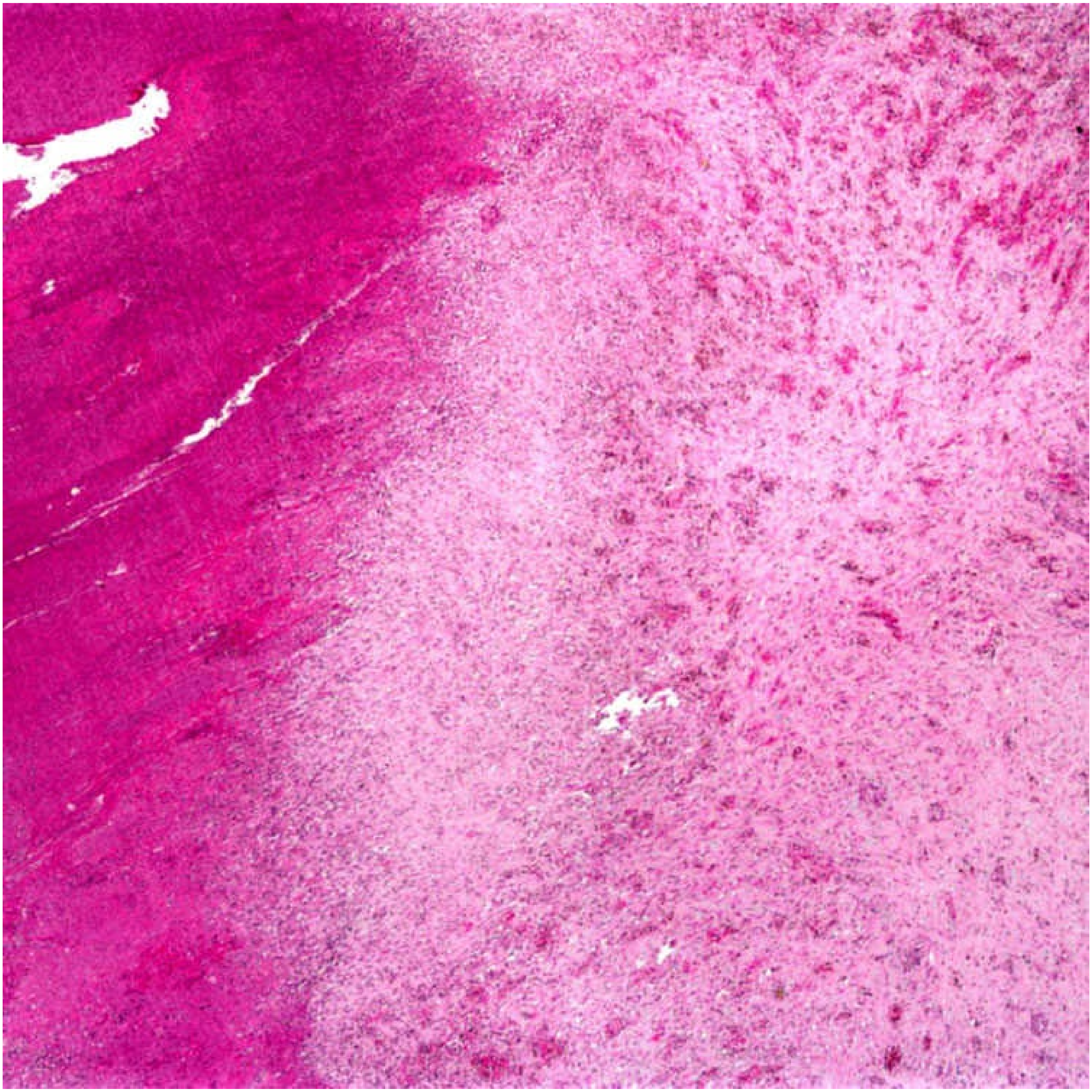
Infarction and Hemorrhage
This hepatocellular adenoma shows infarcted and hemorrhagic appearance.



Ruptured Adenoma
This large adenoma has central areas of rupture and hemorrhage. The patient presented with an acute abdomen.



Infarcted Hepatocellular Adenoma
Degeneration and fibrosis due to infarct in hepatocellular adenoma are shown.



Ruptured Hepatocellular Adenoma
This section from a ruptured hepatocellular adenoma shows hemorrhage on the left and areas of fibrosis and granulation tissue on the right.

SELECTED REFERENCES

1. Nguyen, TB, et al. Combined use of heat-shock protein 70 and glutamine synthetase is useful in the distinction of typical hepatocellular adenoma from atypical hepatocellular neoplasms and well-differentiated hepatocellular carcinoma. *Mod Pathol*. 2016; 29(3):283–292.
2. Colombo, M. Diagnosis of liver nodules within and outside screening programs. *Ann Hepatol*. 2015; 14(3):304–309.
3. Goltz, D, et al. Current Proceedings in the Molecular Dissection of Hepatocellular Adenomas: Review and Hands-on Guide for Diagnosis. *Int J Mol Sci*. 2015; 16(9):20994–21007.

4. Pilati, C, et al. Genomic profiling of hepatocellular adenomas reveals recurrent FRK-activating mutations and the mechanisms of malignant transformation. *Cancer Cell*. 2014; 25(4):428–441.
5. Evason, KJ, et al. Atypical hepatocellular adenoma-like neoplasms with β-catenin activation show cytogenetic alterations similar to well-differentiated hepatocellular carcinomas. *Hum Pathol*. 2013; 44(5):750–758.
6. Bioulac-Sage, P, et al. Revisiting the pathology of resected benign hepatocellular nodules using new immunohistochemical markers. *Semin Liver Dis*. 2011; 31(1):91–103.
7. Bioulac-Sage, P, et al. Pathological diagnosis of liver cell adenoma and focal nodular hyperplasia: Bordeaux update. *J Hepatol*. 2007; 46(3):521–527.
8. Zucman-Rossi, J, et al. Genotype-phenotype correlation in hepatocellular adenoma: new classification and relationship with HCC. *Hepatology*. 2006; 43(3):515–524.
9. Bianchi, L. Glycogen storage disease I and hepatocellular tumours. *Eur J Pediatr*. 1993; 152(Suppl 1):S63–S70.
10. Ferrell, LD. Hepatocellular carcinoma arising in a focus of multilobular adenoma. A case report. *Am J Surg Pathol*. 1993; 17(5):525–529.
11. Flejou, JF, et al. Liver adenomatosis. An entity distinct from liver adenoma? *Gastroenterology*. 1985; 89(5):1132–1138.
12. Edmondson, HA, et al. Liver-cell adenomas associated with use of oral contraceptives. *N Engl J Med*. 1976; 294(9):470–472.

Focal Nodular Hyperplasia

KEY FACTS

Terminology

- Benign tumor-like lesion of liver caused by hyperplastic response to localized vascular abnormality

Clinical Issues

- Mostly incidental finding on imaging studies, most common in women

Macroscopic

- Unencapsulated, well-circumscribed lesion with bulging cut surface
  - Noncirrhotic background liver
- Central stellate scar with radiating septa

Microscopic

- Localized nodular parenchyma with fibrous septa and stellate central scar
  - Septa contain thick-walled vessels and mononuclear inflammatory infiltrate
- Ductular reaction at junction between septa and parenchyma

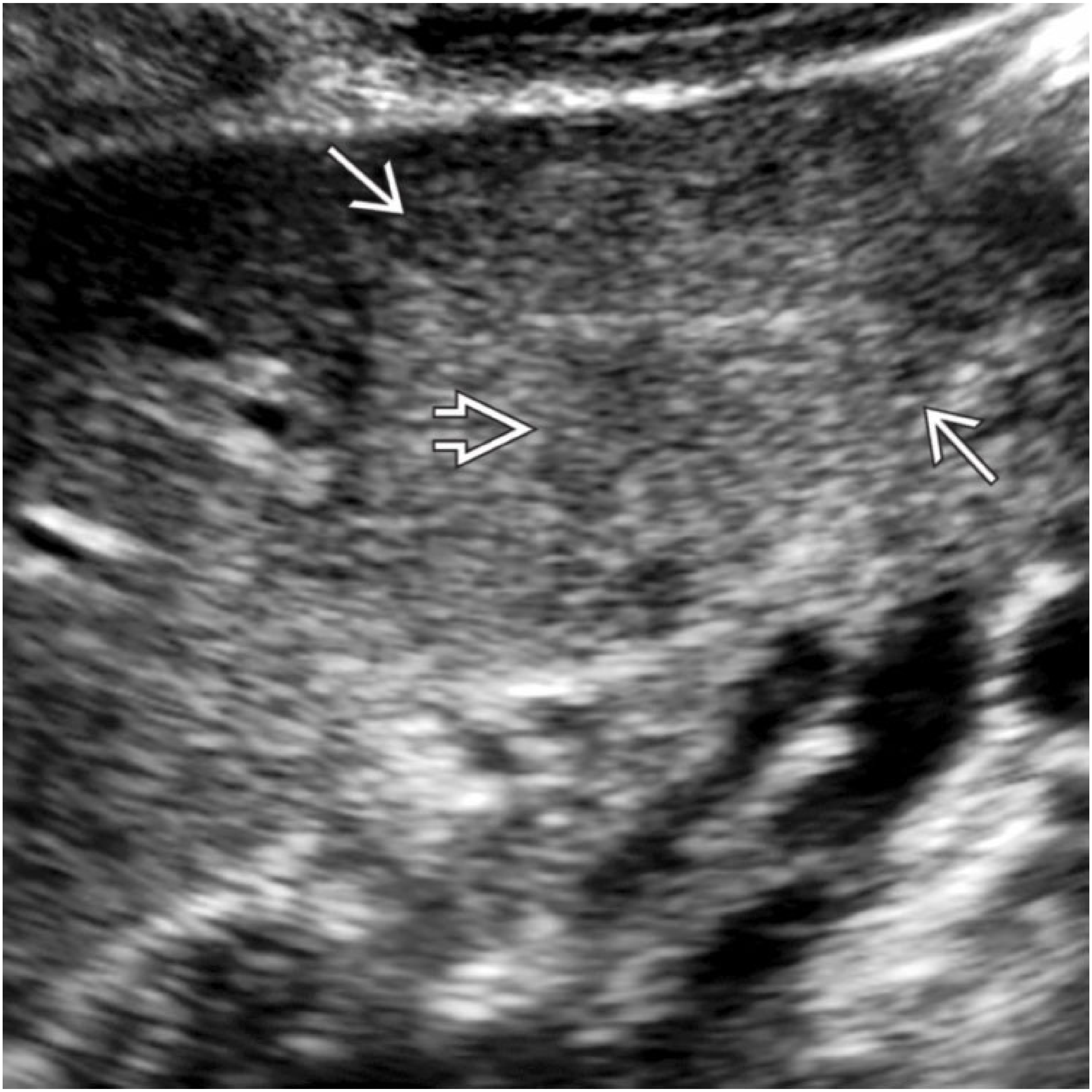
Ancillary Tests

- Glutamine synthetase: Characteristic map-like pattern, with sparing of areas around scar and fibrous septa
- Serum amyloid A is typically negative; focal staining in few case
- C-reactive protein staining typically restricted to periseptal areas

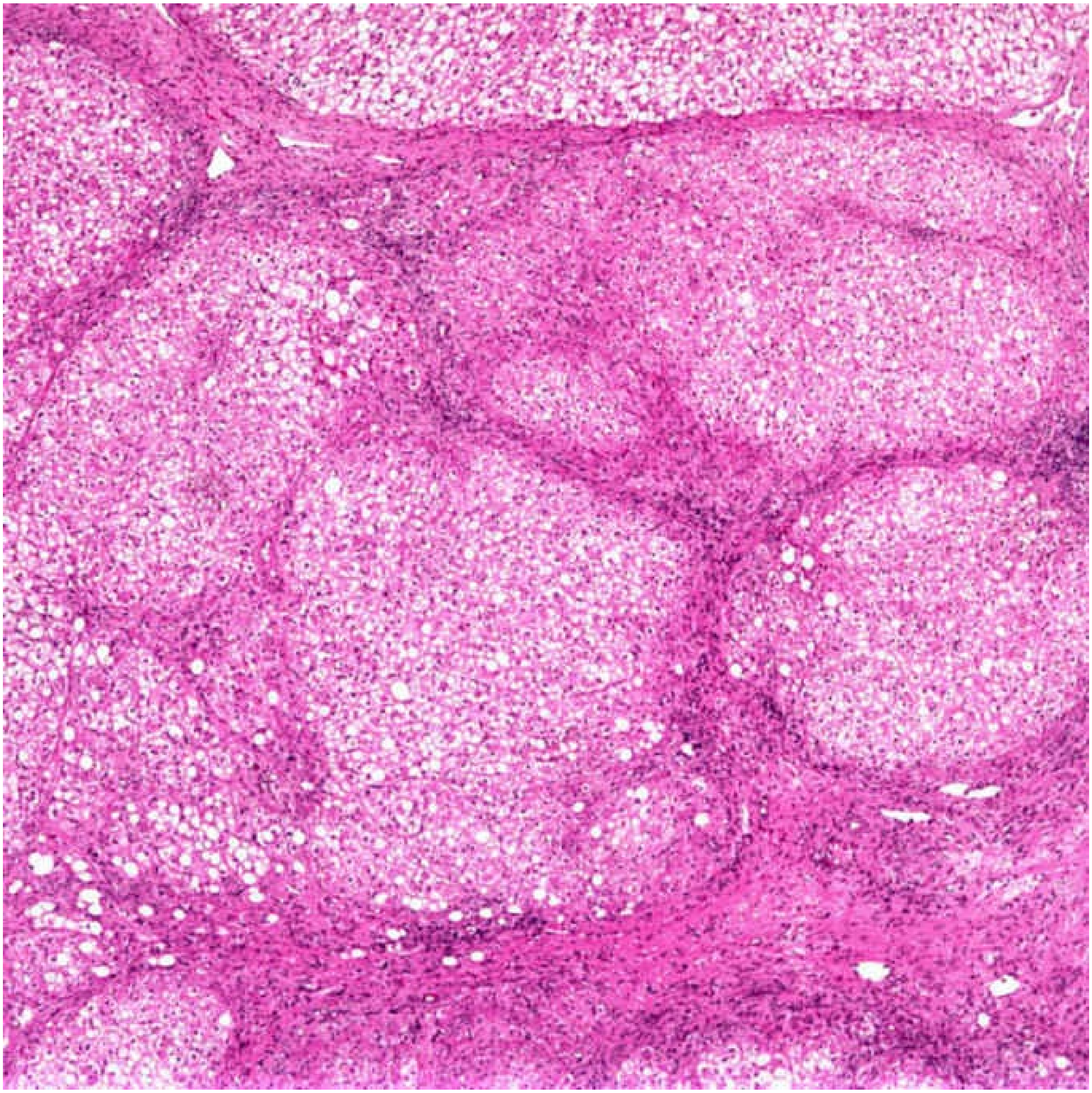
Top Differential Diagnoses

- Hepatocellular adenoma
- Cirrhosis

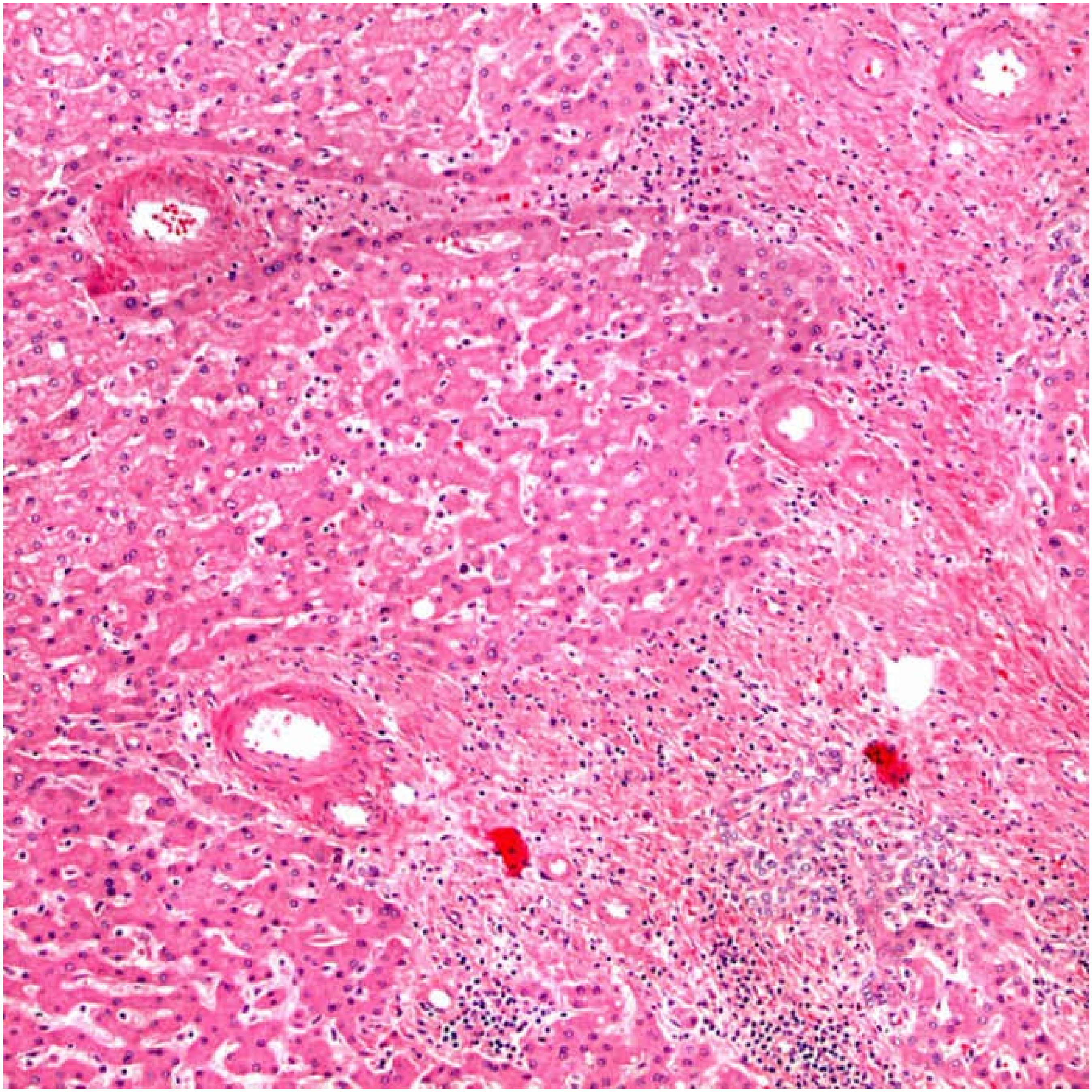
• Hepatocellular carcinoma
• Nodular regenerative hyperplasia



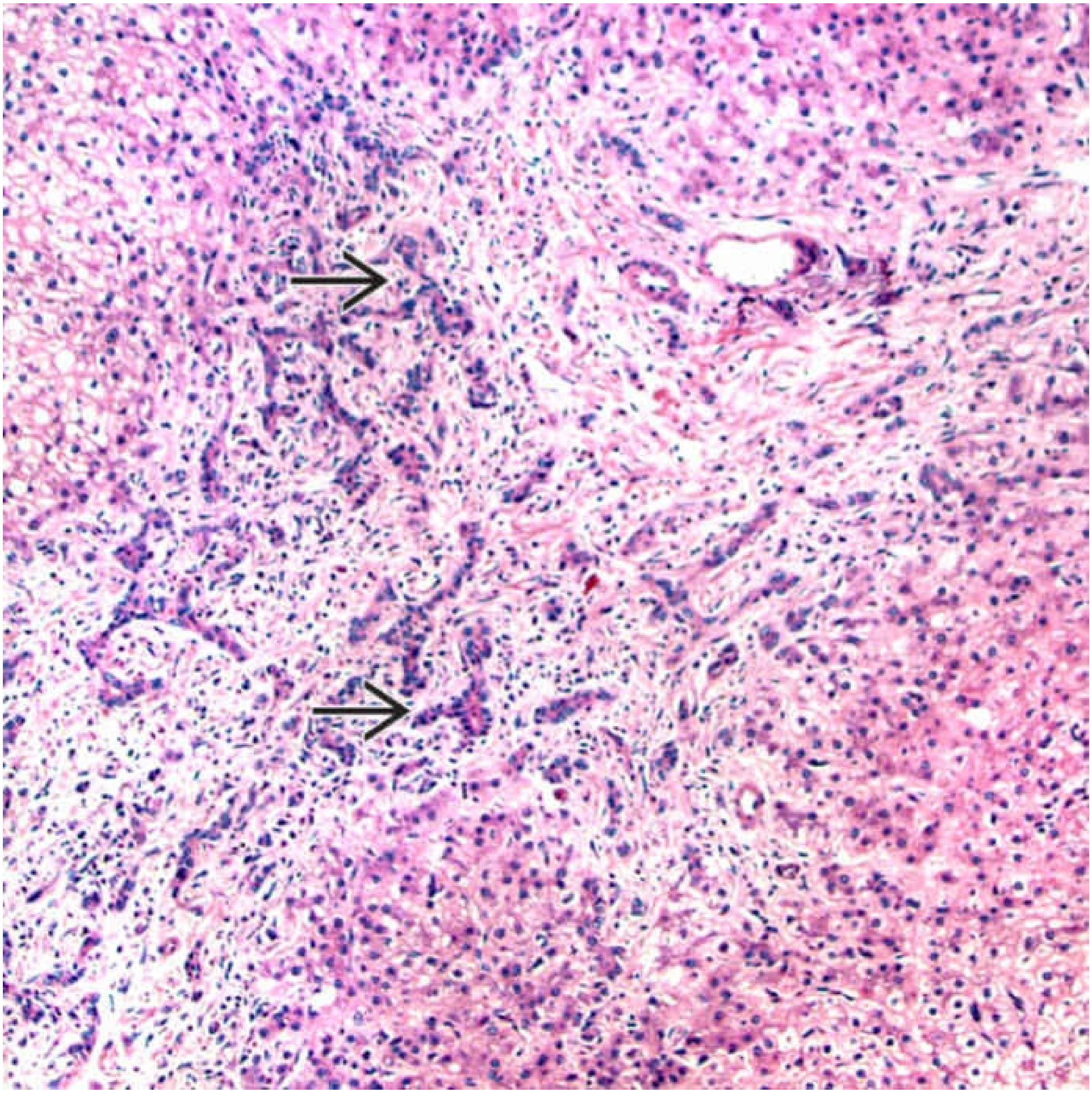
Ultrasound Findings
Oblique transabdominal ultrasound shows a hypoechoic central scar in the center of an isoechoic mass (FNH). The scar may show vascular calcification but the lesion itself rarely calcifies.



Nodular Architecture
Low-power photomicrograph of focal nodular hyperplasia shows the nodular hepatic parenchyma separated by fibrous septa. This appearance can mimic biliary cirrhosis.



Aberrant Arterioles
Thick-walled arteries are typically seen at the periphery of the fibrous septa in FNH. Less commonly, the aberrant arterioles can be seen in the parenchyma.



Ductular Reaction
FNH typically shows a marked ductular reaction → in the fibrous septa. By definition, normal interlobular bile ducts and normal portal tract are absent.

TERMINOLOGY

Abbreviations

• Focal nodular hyperplasia (FNH)

Synonyms

• Focal cirrhosis

Definitions

- Benign tumor-like lesion caused by hyperplastic response to localized vascular abnormality
- Most lesions formerly labeled as telangiectatic FNH are thought to be inflammatory hepatocellular adenomas

ETIOLOGY/PATHOGENESIS

Localized Abnormal Blood Flow

- Exact mechanism unclear
- Hepatocytes polyclonal, unlike hepatocellular adenomas
- Steroids are not thought to play role

CLINICAL ISSUES

Presentation

- Mostly incidental finding on imaging studies
- More common in women
- Normal liver biochemical tests

Treatment

- Surgical approaches
    - Reserved for large and symptomatic lesions

Prognosis

- Benign lesion; rupture and bleeding in rare cases

IMAGING

General Features

- Brightly, homogeneously enhancing mass in arterial phase CT or MR with delayed enhancement of central scar

MACROSCOPIC

General Features

- Unencapsulated, well-circumscribed lesion
    - ~ 20% are multiple
- Firm to rubbery cut surface that bulges from surface of liver
- Central stellate scar with radiating septa
- Noncirrhotic background liver

Size

- Most < 5 cm

MICROSCOPIC

Histologic Features

- Nodular architecture
- Fibrous septa, usually with large central stellate scar
- Ductular reaction in fibrous septa
- Dilated sinusoids and lymphocytic infiltrate may be present
- Periseptal hepatocytes may show positive copper staining due to cholestasis
- Reticulin is intact, but wide plates and focal loss can be seen at periphery

Cytologic Features

- Bland hepatocytes

ANCILLARY TESTS

Immunohistochemistry

- Glutamine synthetase (GS): Characteristic map-like pattern with sparing of areas around scar and fibrous septa
- CK7: Highlights ductular reaction, typically negative in lesional hepatocytes
- CD34: Patchy sinusoidal staining, can be variably diffuse
- Serum amyloid A (SAA): Negative, focally positive in few cases
- C-reactive protein (CRP): Staining usually restricted to periseptal areas

DIFFERENTIAL DIAGNOSIS

Inflammatory Hepatocellular Adenoma

- Histologic features overlap with FNH
- Naked unpaired arteries in parenchyma, sinusoidal dilatation, and lesional steatosis more common in adenoma
- Ductular reaction, fibrous septa, and thick-walled arteries are more common in FNH
- Diffuse immunoreactivity for SAA and CRP in most cases
- Map-like GS staining not seen

Cirrhosis

- Diffuse liver involvement
- Ductular reaction and inflammation may be present in fibrous septa

- Bile ducts present except in ductopenic biliary disease
- Lack of thick-walled arteries
- Evidence of underlying liver disease

Hepatocellular Carcinoma

- Thick cell plates, reticulin loss
- Cytologic atypia variable but often present
- Ductular reaction not present in tumor
- Diffuse GS, positive glypican-3, HSP70

Nodular Regenerative Hyperplasia

- Nodularity is typically diffuse
- By definition, fibrous septa are not present

FNH-Like Lesion

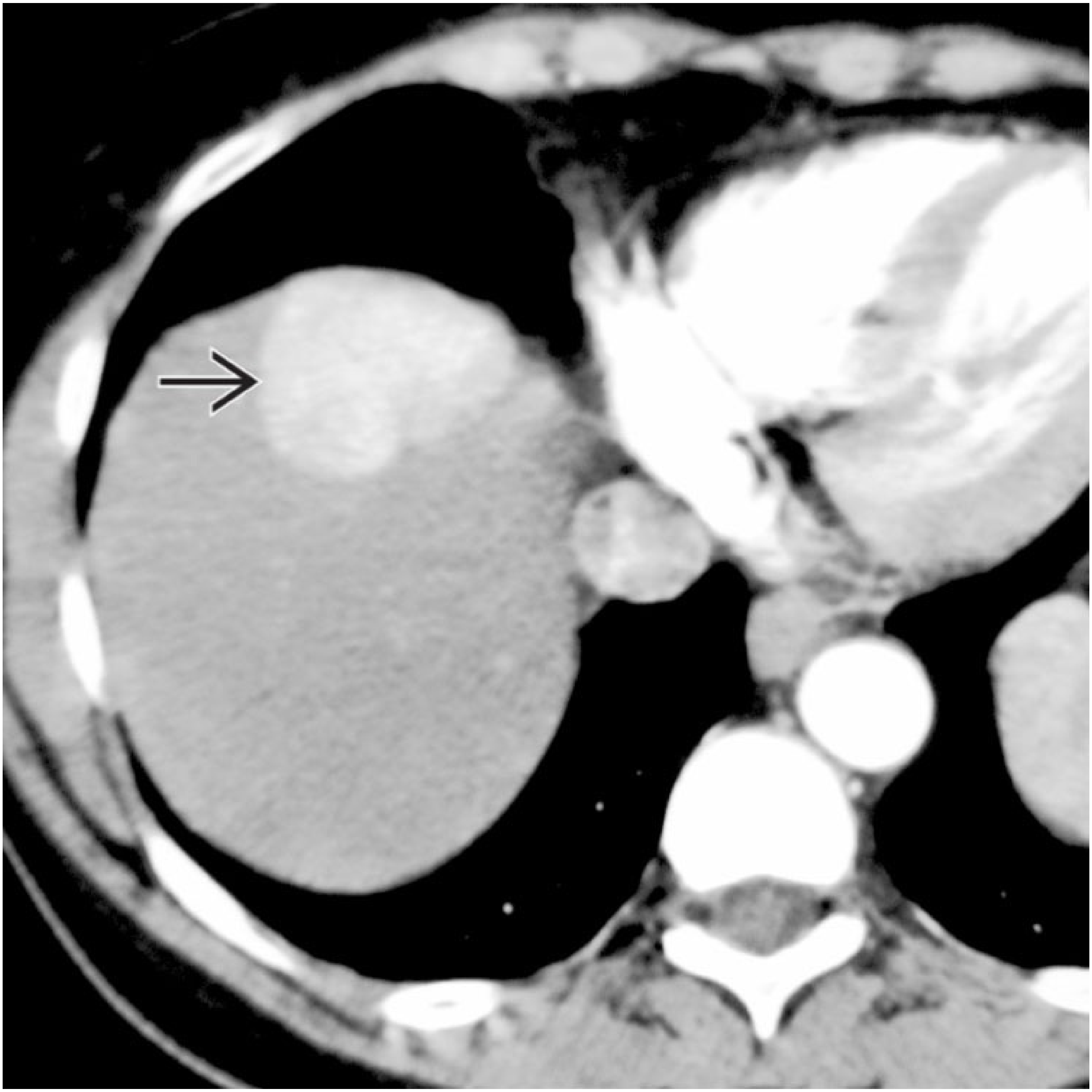
- Histologic features indistinguishable from FNH
    - Associated with other disease processes
        - Vascular diseases: Budd-Chiari syndrome, cavernous hemangioma, Osler-Weber-Rendu disease (hereditary hemorrhagic telangiectasia)
        - Adjacent to other tumors, primary or metastatic
        - May occur in cirrhotic liver

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

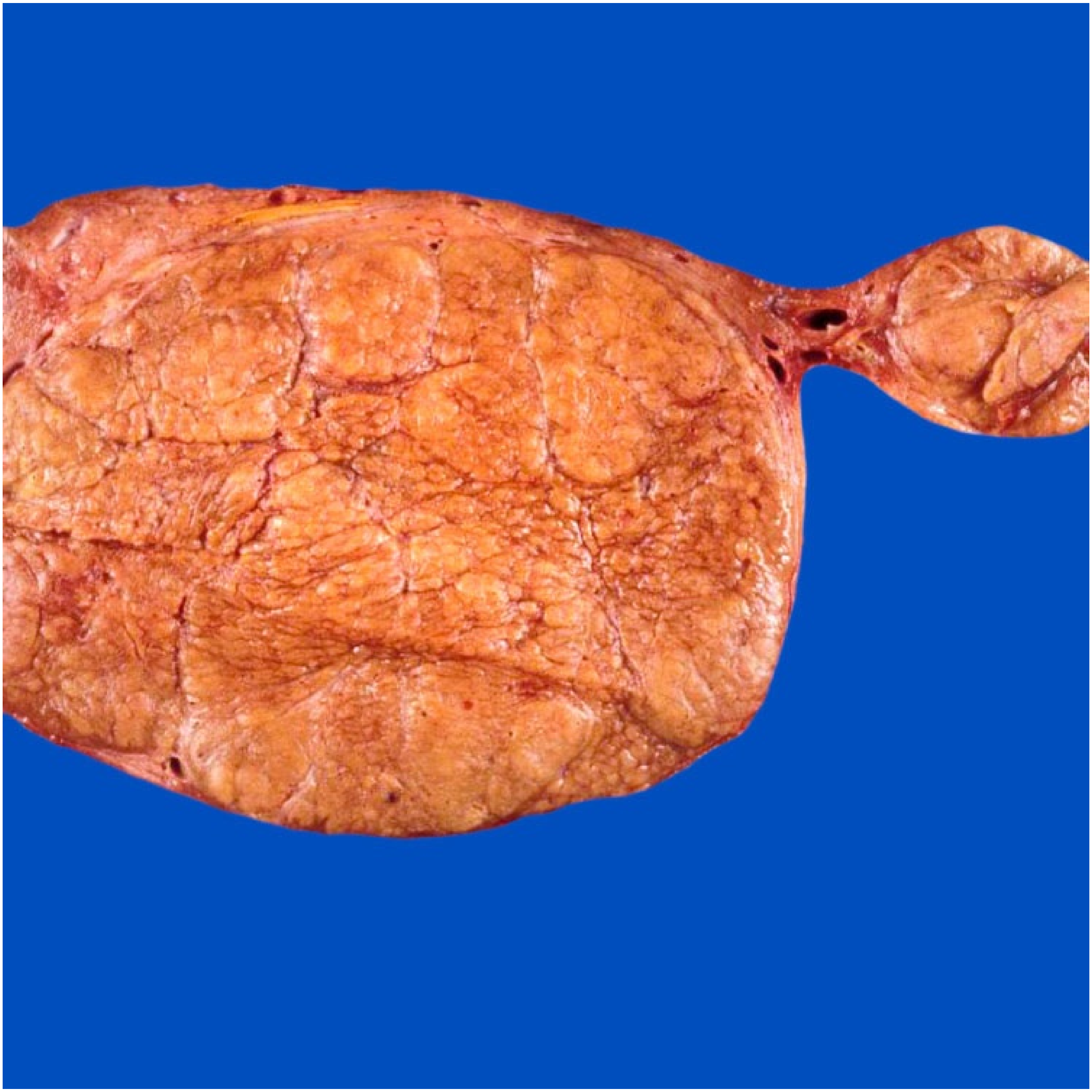
- Nodular liver parenchyma with fibrous septa containing thick-walled arteries at periphery, bile ductular reaction, and mixed mononuclear inflammation

Central Scar
Wedge liver resection shows a well-circumscribed, nodular lesion with a central stellate scar →. This is a hallmark of FNH but may not be seen in up to 1/3 of cases.

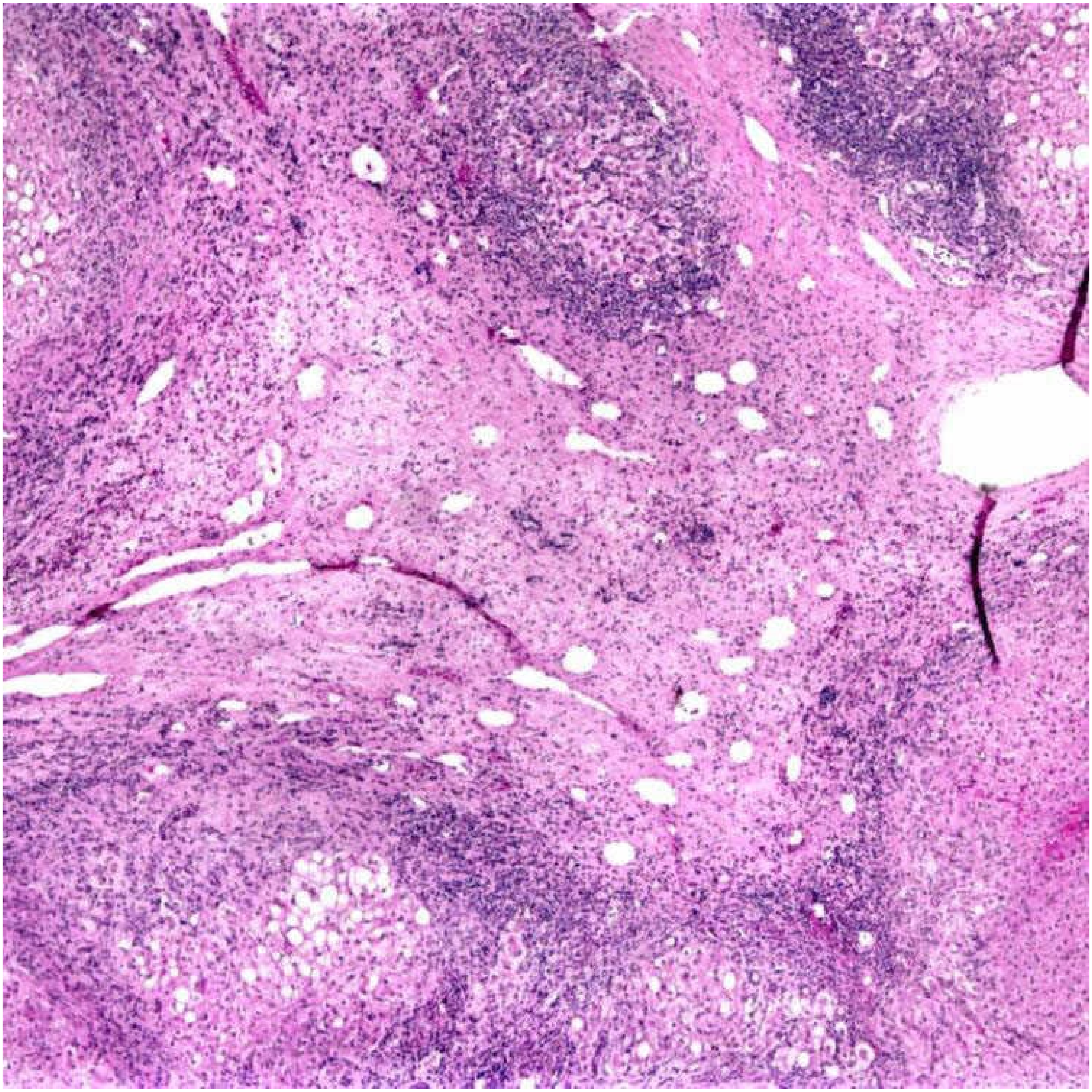


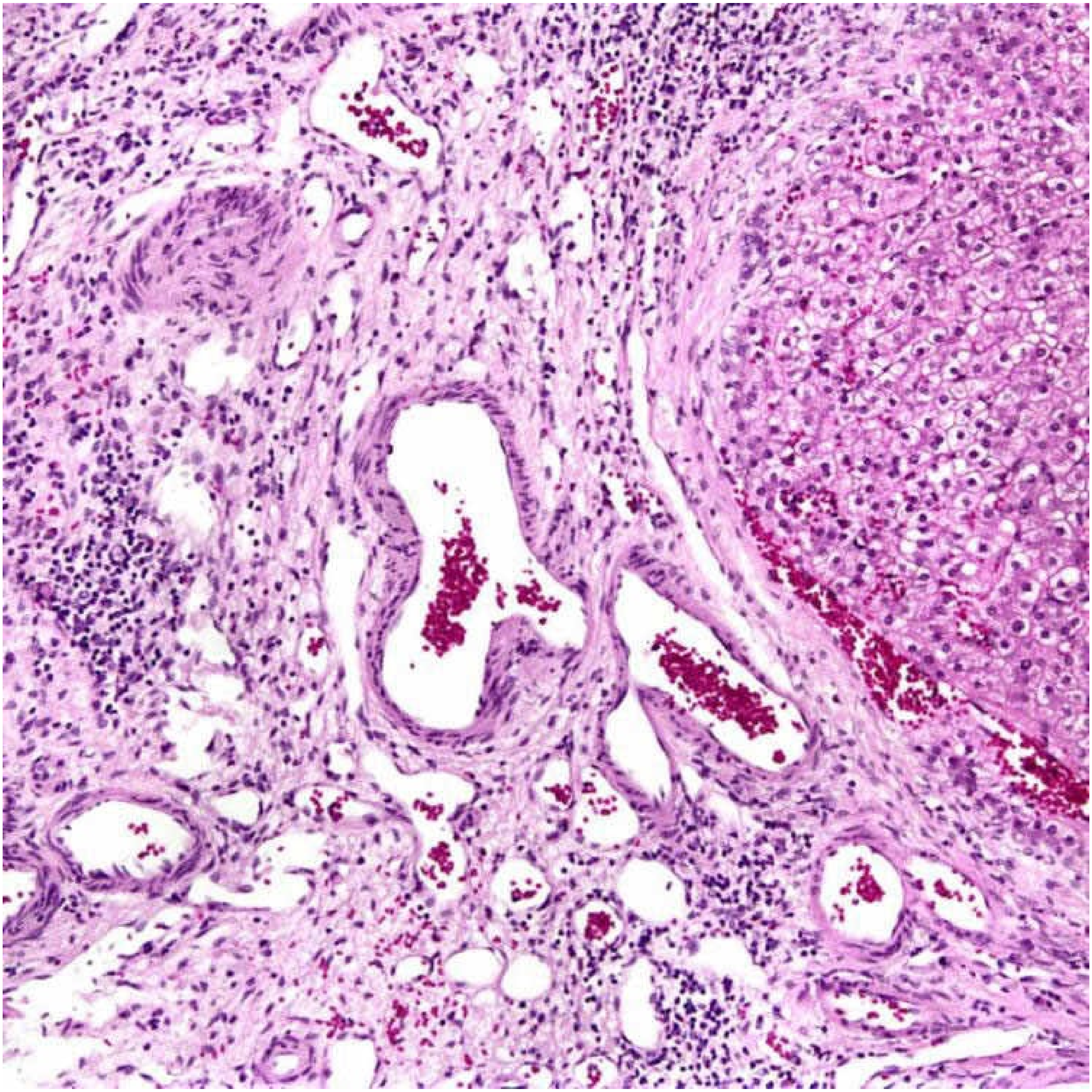
CT Scan

Axial CECT during the arterial phase shows a subcapsular enhancing hepatic mass without a central scar →.

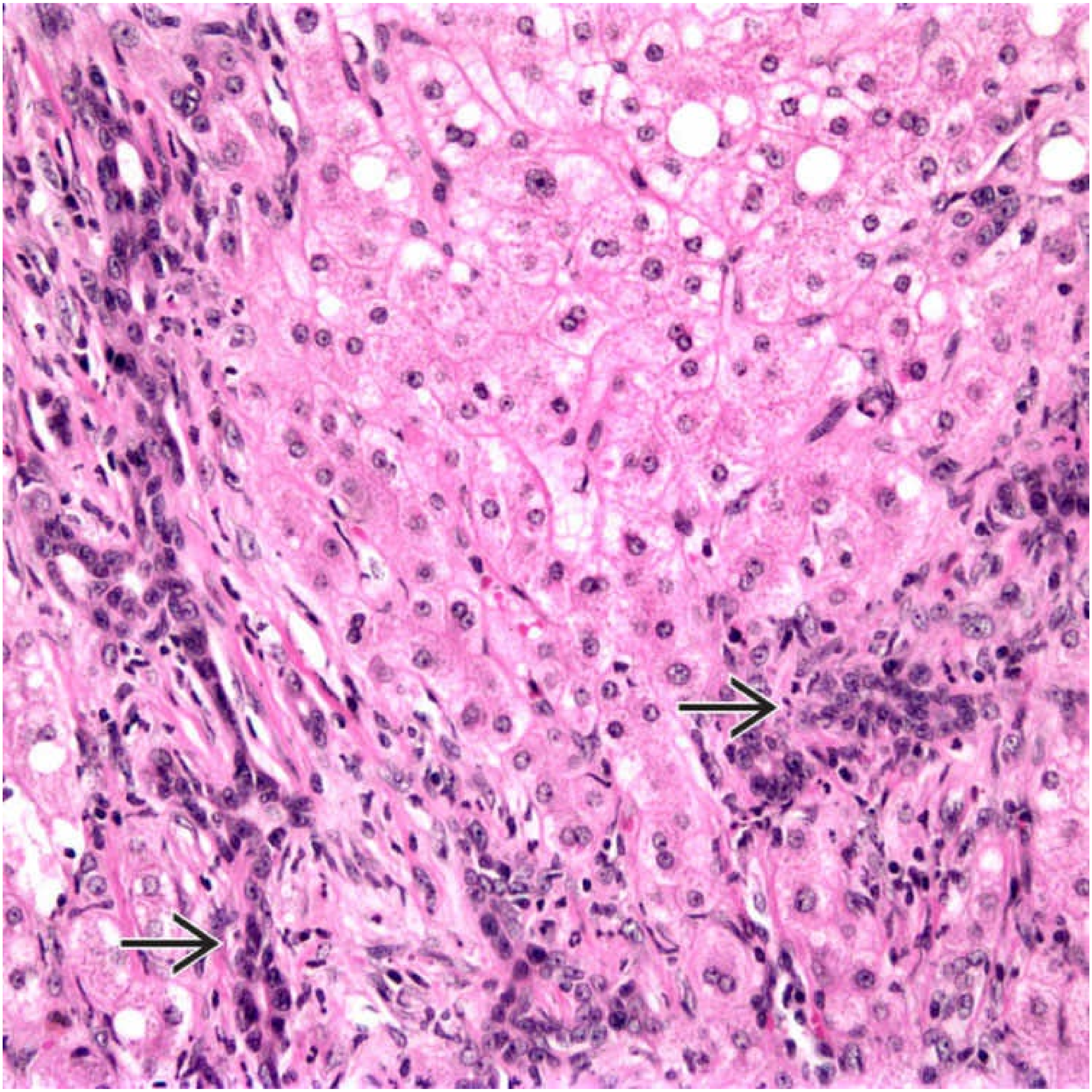


Multiple Focal Nodular Hyperplasia
Focal nodular hyperplasia is typically solitary, but multiple lesions can be present, sometimes in association with vascular disorders like Budd-Chiari syndrome or hereditary hemorrhagic telangiectasia.


Central Scar
Typical central scar shows prominent arteriole, lymphocytic inflammation, and nodular architecture.

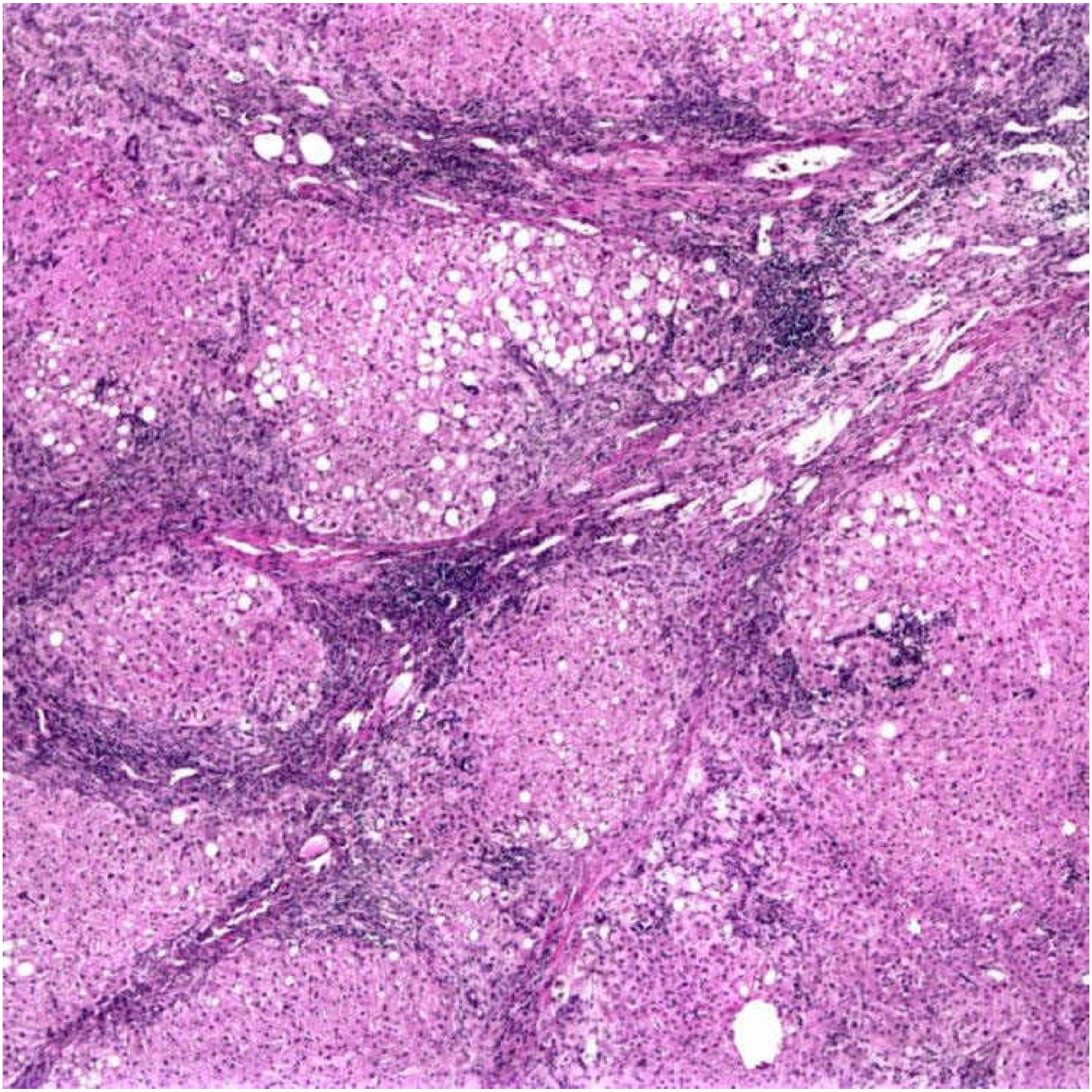


Focal Nodular Hyperplasia
Cluster of aberrant arterioles is shown in the central scar. Eccentric intimal thickening and medial hypertrophy can occur. Ductular reaction is not prominent in this case, a feature that is well described in FNH.



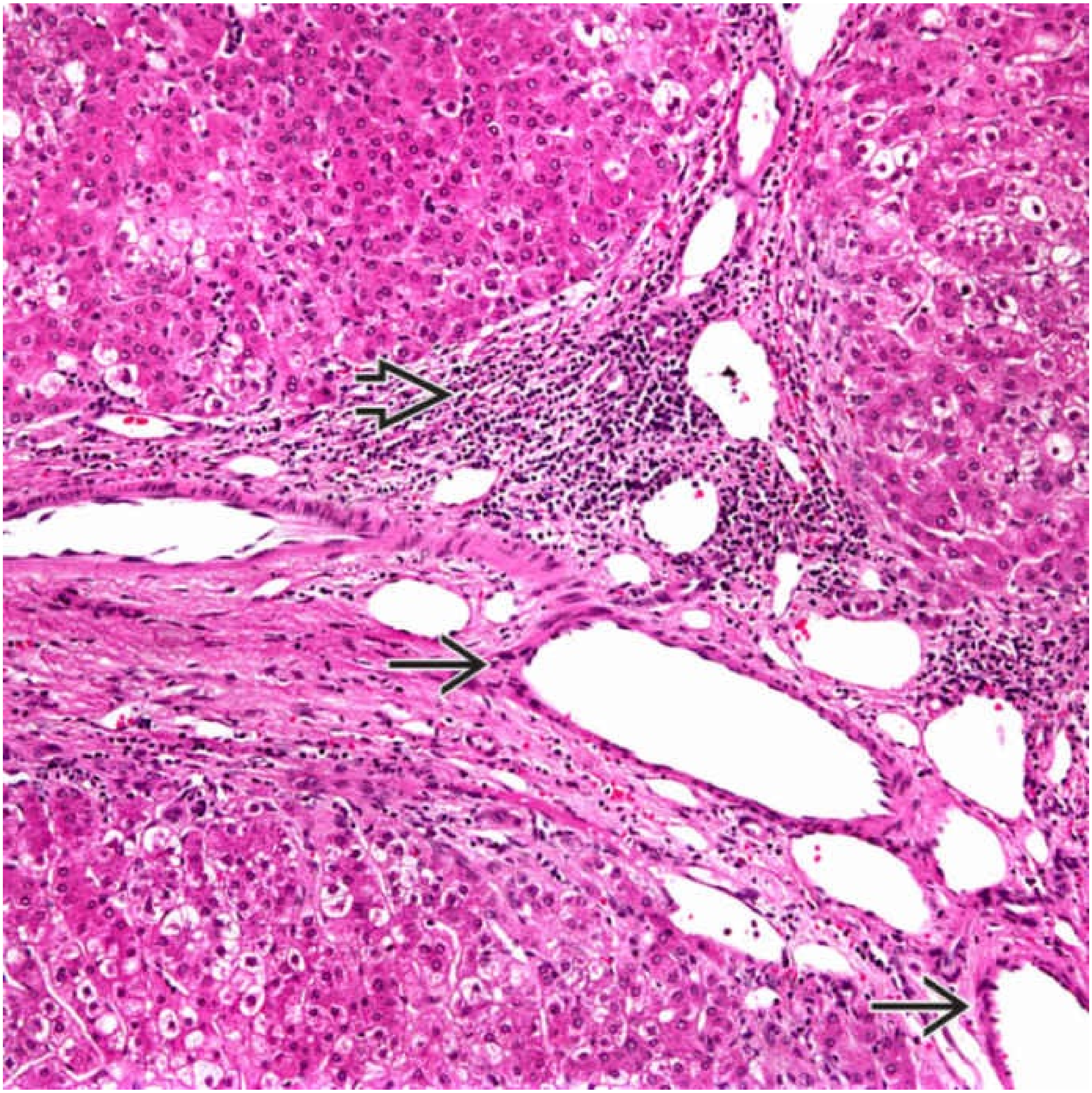
Ductular Reaction

High-power view demonstrates the ductular reaction →. In a minority of cases, ductular reaction is minimal and can create diagnostic problems. The lesional hepatocytes lack cytologic or architectural atypia.



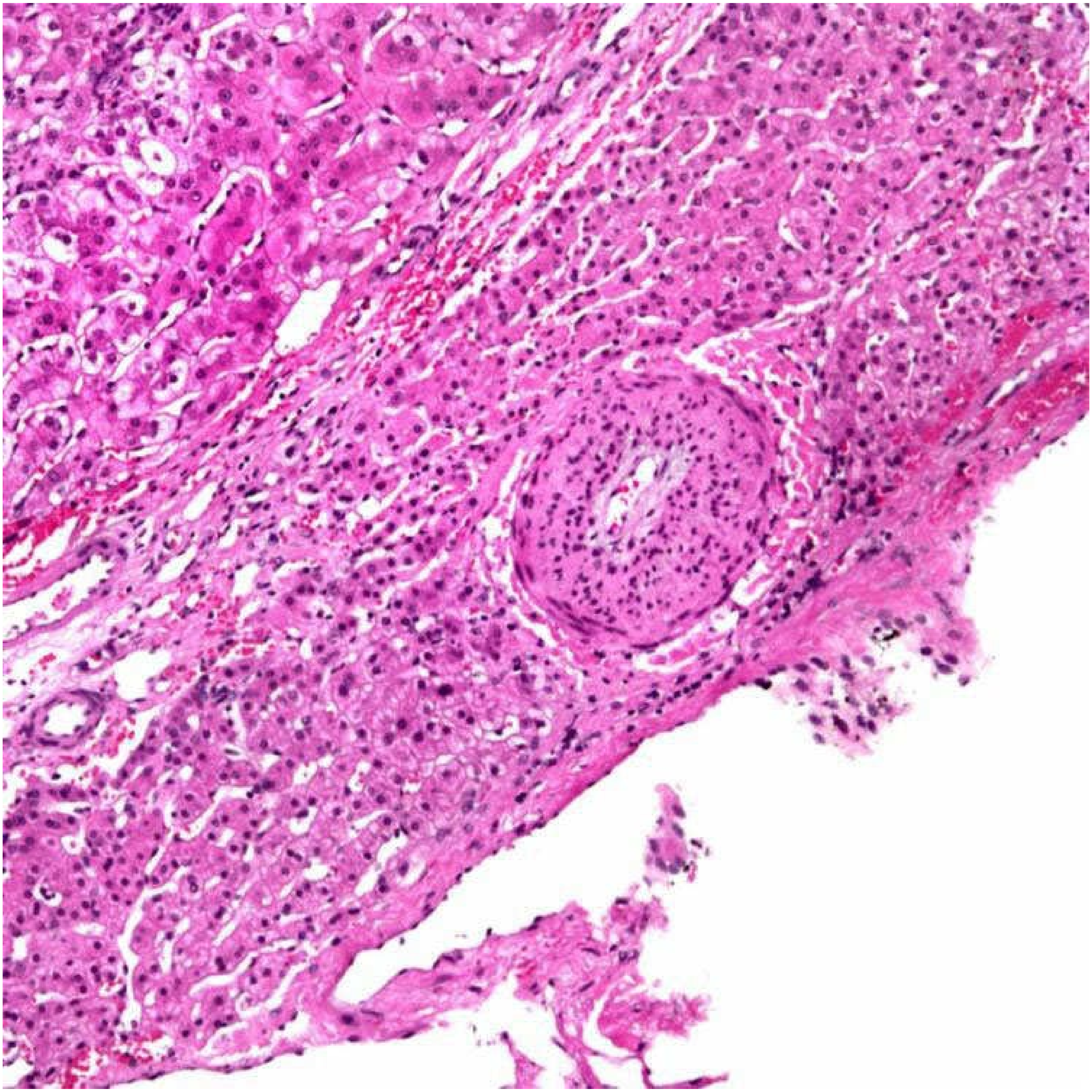
Lesional Fat

Typical findings of FNH are evidenced by nodular architecture and fibrous septa. Lesional fat is typically minimal or absent, but significant steatosis can be seen in 20% of cases, while rare cases can show steatohepatitic changes with ballooned lesional hepatocytes and Mallory hyaline.

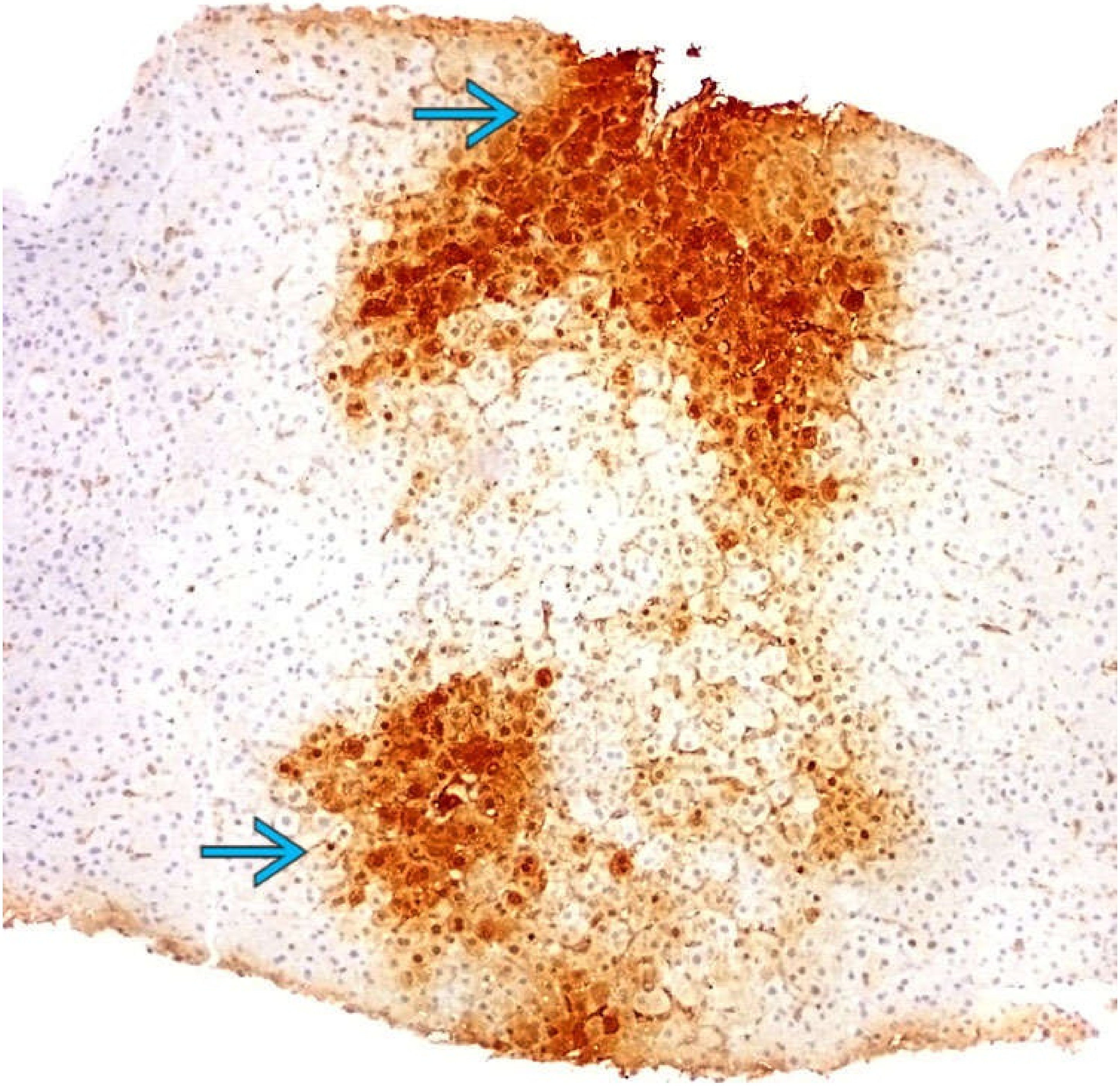


Mild Inflammation

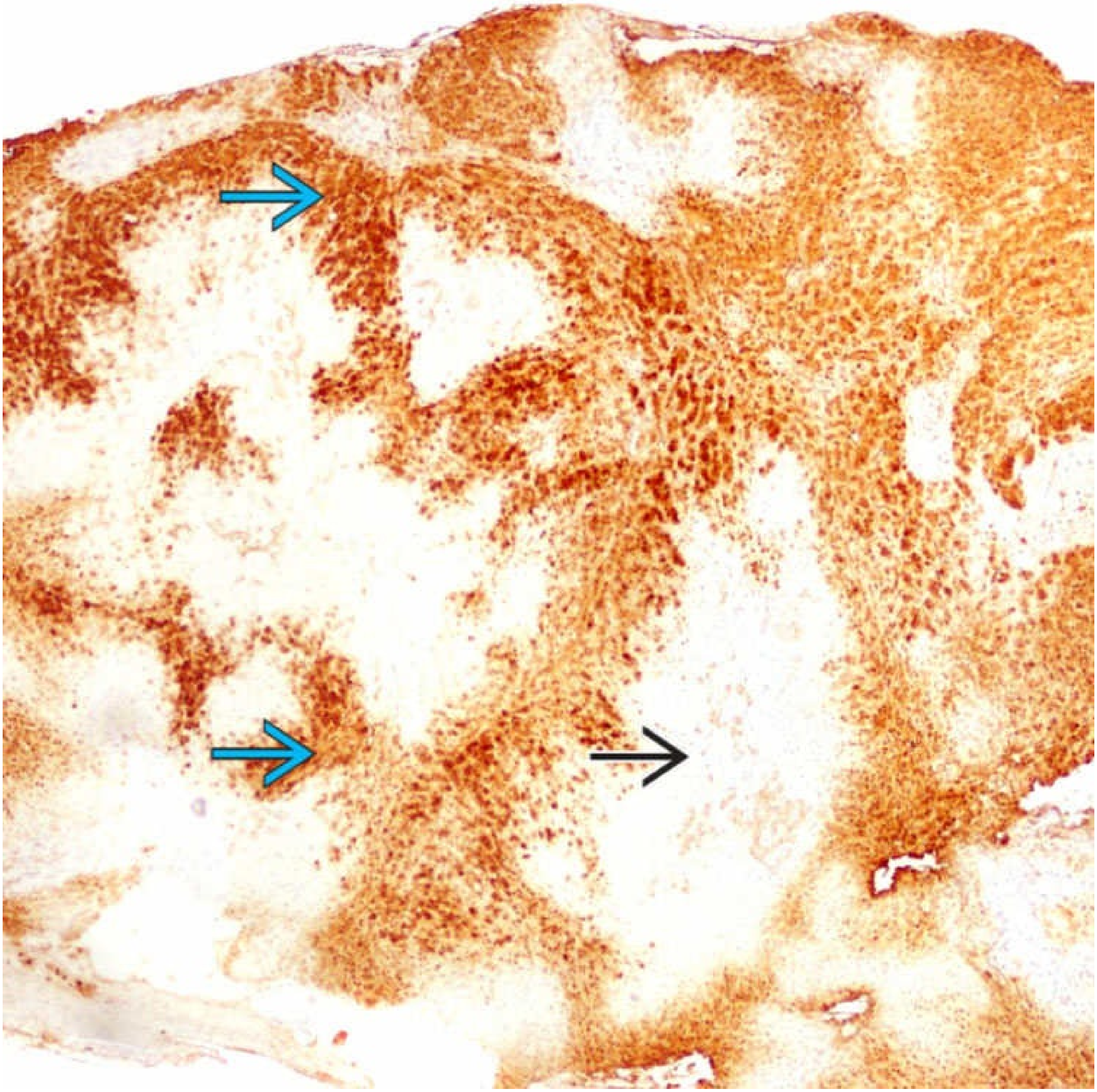
Fibrous septa show aberrant vessels →, and a mild lymphocytic infiltrate can be present ⇨. The inflammatory component is variable in FNH, being absent or mild in most cases.



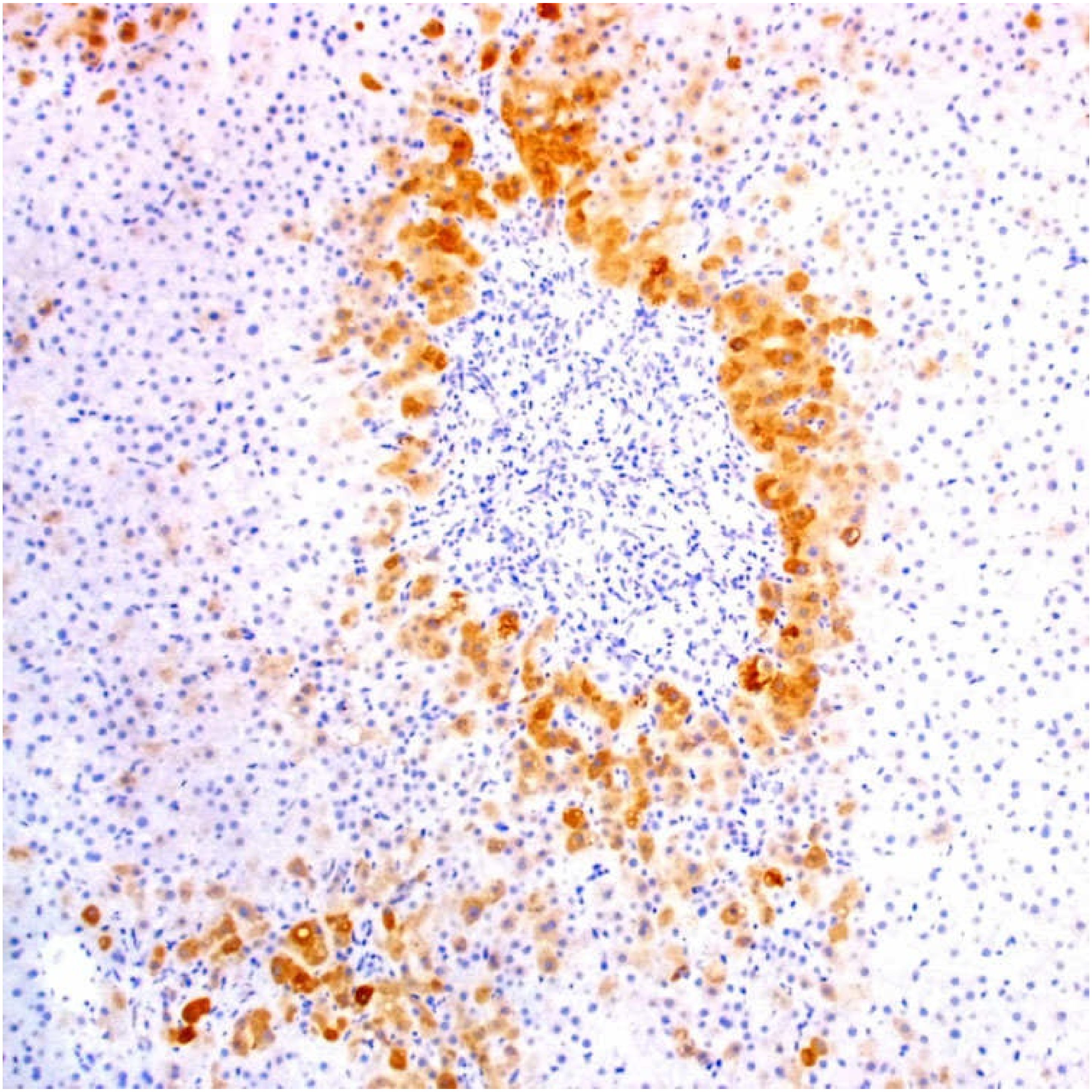
Aberrant Arteriole
Thick-walled arterioles unaccompanied by interlobular bile ducts (“naked” or “unpaired” arteriole) is a hallmark of FNH. Ductular reaction is absent in this case.



Glutamine Synthetase, Normal Liver
Immunohistochemistry for glutamine synthetase in normal liver shows staining of 2-3 rims of hepatocytes → in the centrizonal region.



Glutamine Synthetase, Map-Like Pattern
Immunohistochemistry for glutamine synthetase shows a highly characteristic, map-like staining pattern due to broad anastomosing bands of positively stained lesional hepatocytes →. The central scar and variably sized regions around fibrous septa → can be negative.



C-Reactive Protein, Periseptal Staining
Immunohistochemistry for C-reactive protein in FNH typically shows staining of hepatocytes around the fibrous septa. Less commonly, a more diffuse staining pattern can be observed.

SELECTED REFERENCES

1. Joseph, NM, et al. Diagnostic utility and limitations of glutamine synthetase and serum amyloid-associated protein immunohistochemistry in the distinction of focal nodular hyperplasia and inflammatory hepatocellular adenoma. *Mod Pathol*. 2014; 27(1):62–72.
2. Ahmad, I, et al. Diagnostic use of cytokeratins, CD34, and neuronal cell adhesion molecule staining in focal nodular hyperplasia and hepatic adenoma. *Hum Pathol*. 2009; 40(5):726–734.
3. Bioulac-Sage, P, et al. Pathological diagnosis of liver cell adenoma and focal nodular hyperplasia: Bordeaux update. *J Hepatol*. 2007; 46(3):521–527.

4. Makhlouf, HR, et al. Diagnosis of focal nodular hyperplasia of the liver by needle biopsy. *Hum Pathol*. 2005; 36(11):1210–1216.
5. Kondo, F. Benign nodular hepatocellular lesions caused by abnormal hepatic circulation: etiological analysis and introduction of a new concept. *J Gastroenterol Hepatol*. 2001; 16(12):1319–1328.
6. Nguyen, BN, et al. Focal nodular hyperplasia of the liver: a comprehensive pathologic study of 305 lesions and recognition of new histologic forms. *Am J Surg Pathol*. 1999; 23(12):1441–1454.
7. Wanless, IR, et al. On the pathogenesis of focal nodular hyperplasia of the liver. *Hepatology*. 1985; 5(6):1194–1200.

Regenerative and Dysplastic Nodules

KEY FACTS

Clinical Issues

- Regenerative nodule (RN): Cirrhotic nodule > 1 cm; most believed to be nonneoplastic
  - Low-grade dysplastic nodules (LGDNs) resemble RN morphologically but are clonal
- High-grade dysplastic nodules (HGDNs): Preneoplastic lesion; likely precursor of hepatocellular carcinoma (HCC)

Macroscopic

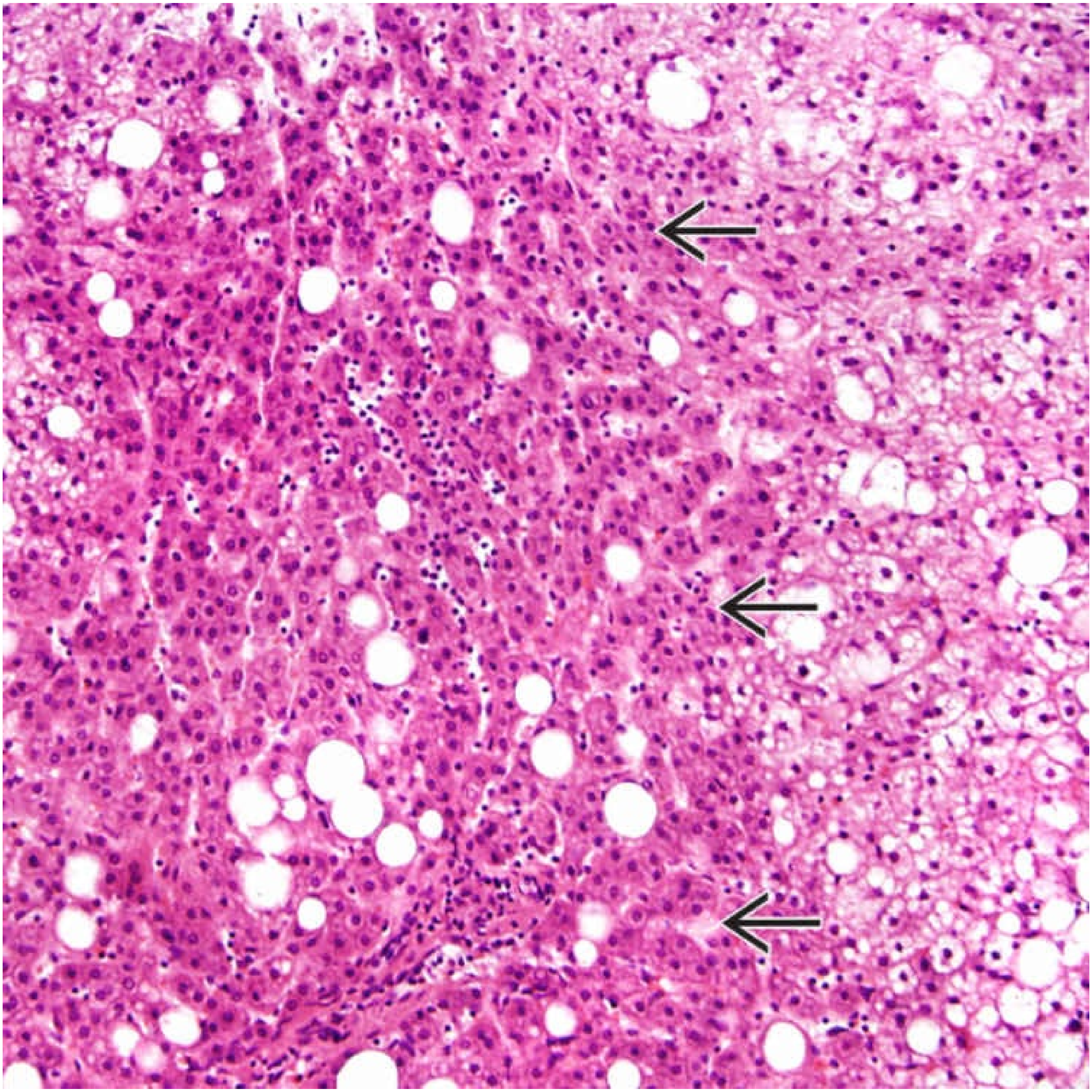
- > 1 cm but usually < 3 cm

Microscopic

- RN/LGDN: Plates 1-2 cells thick, portal tracts present, no architectural or cytologic atypia
  - HGDN: Plates focally up to 3 cells thick; small cell change with increased nuclear:cytoplasmic ratio
  - Unpaired arterioles and pseudoacinar architecture can be present
- Reticulin is preserved
  - May be focally lost in HGDN

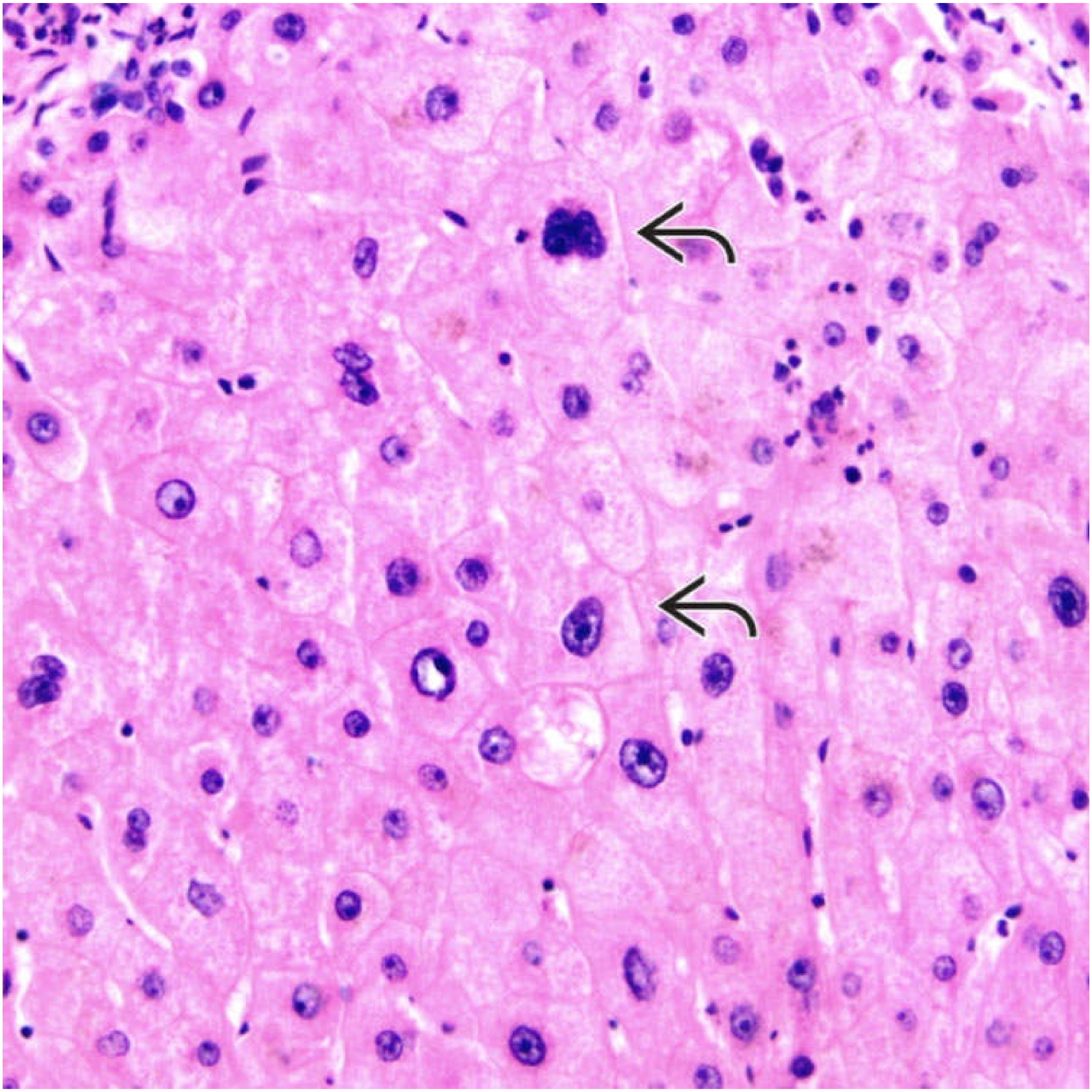
Top Differential Diagnoses

- Small cell change, high nuclear:cytoplasmic ratio, pseudoacinar architecture, and unpaired arterioles favor HGDN over LGDN
  - Uniformly thick plates (> 3 cells) are most important feature distinguishing HCC from HGDN
  - Prominent pseudoacinar architecture, numerous unpaired arterioles, and loss or fragmentation of reticulin favor HCC
- Stromal invasion distinguishes early HCC from HGDN
  - Lack of CK7(+) ductular reaction is useful in demonstrating stromal invasion
- Positive results with 2 out of 3 markers (GPC, GS, HSP70) favor HCC

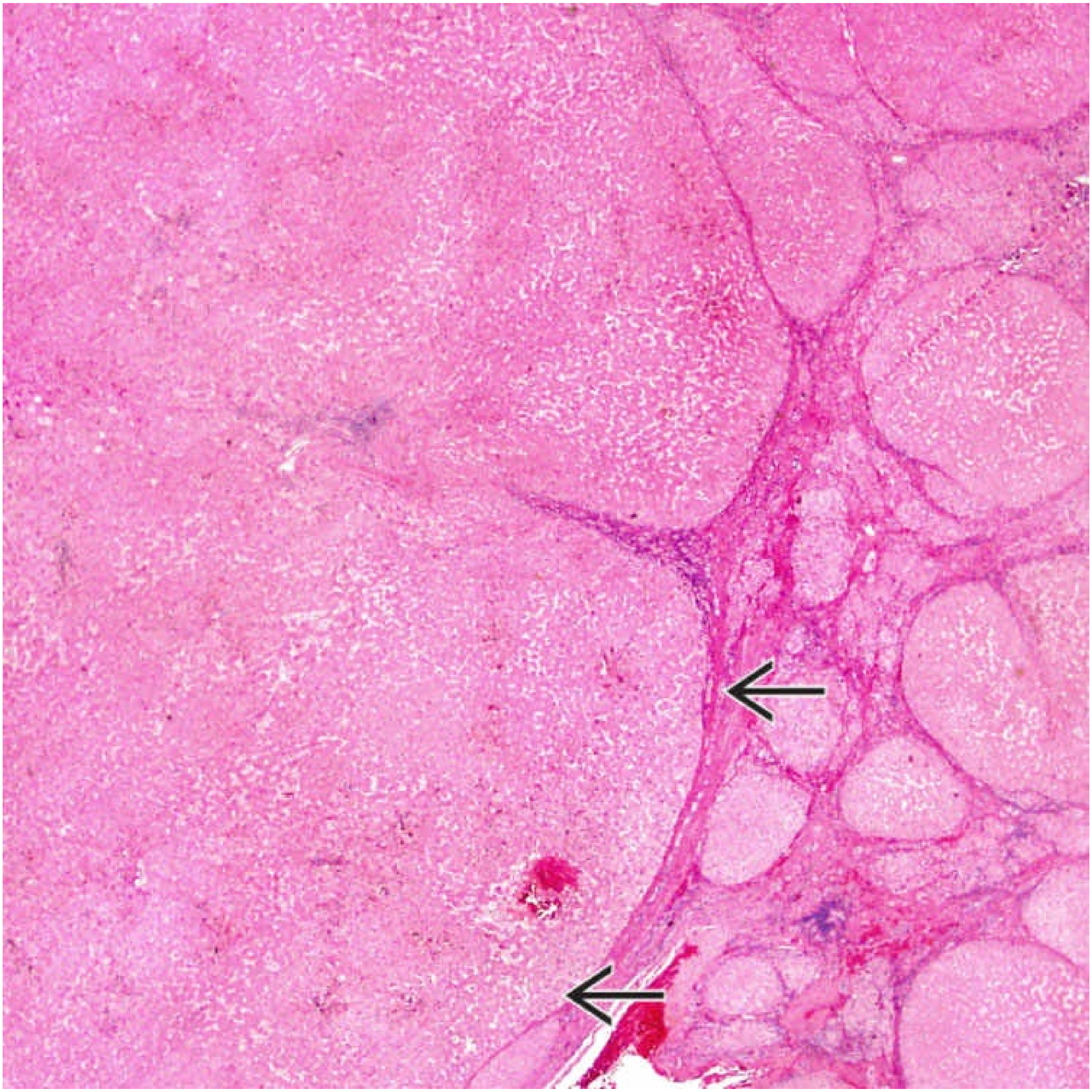


Small Cell Change

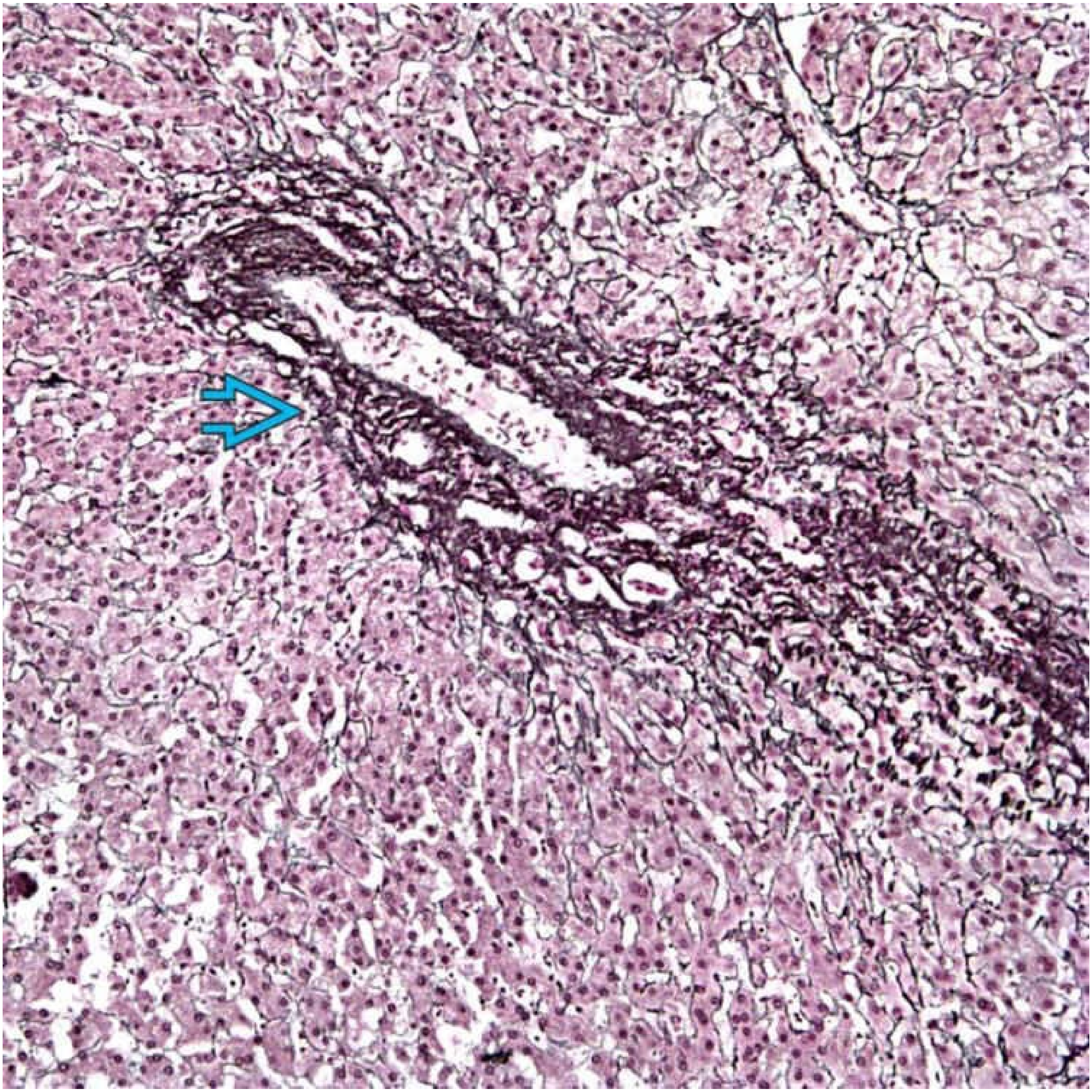
Small cell change (left 2/3 of image) → is characterized by small cells with high nuclear:cytoplasmic ratio leading to increased cell density. When present in a nodule, it is the hallmark of high-grade dysplastic nodule (HGDN).



Large Cell Change
Large cell change is characterized by large hyperchromatic nuclei but preserved nuclear:cytoplasmic ratio ↷. This change is thought to be degenerative and not preneoplastic.



Large RN
Large regenerative nodules (RNs) → resemble other cirrhotic nodules but are > 1 cm. Ductular reaction is usually present at the interface of the nodule with the fibrous septa.



RN: Reticulin Stain
Regenerative nodule containing a portal tract and an intact reticulin framework is shown. These features and the absence of cytoarchitectural atypia distinguish it from dysplastic nodule and hepatocellular carcinoma (HCC).

TERMINOLOGY

Abbreviations

- Regenerative nodule (RN), large regenerative nodule (LRN), low-grade dysplastic nodule (LGDN), high-grade dysplastic nodule (HGDN)

Synonyms

- Macroregenerative nodule (MRN), adenomatous hyperplasia
- Borderline nodule, type II MRN, atypical adenomatous hyperplasia, atypical MRN

Definitions

- Dysplasia: Abnormal histologic growth that does not fulfill criteria of malignancy
  - Dysplastic focus: Cluster of dysplastic hepatocytes < 1 cm in diameter
  - Dysplastic nodule: Cluster of dysplastic hepatocytes > 1 cm in diameter
- LRN: > 1 cm, usually seen in cirrhosis
  - No reliable gross or histologic criteria to distinguish RN and LGDN
    - LGDN is clonal proliferation; likelihood of progression to carcinoma is unclear
  - Most RN are probably not preneoplastic
- HGDN: Nodule with atypical cytologic and architectural features believed to be precursor of carcinoma
- Large cell change (formerly large cell dysplasia)
  - Large hepatocytes with nuclear enlargement, hyperchromasia, prominent nucleoli, often multinucleated
    - Abundant cytoplasm, normal nuclear:cytoplasmic ratio
  - Very common in cirrhotic liver
  - Formerly thought to be precursor of hepatocellular carcinoma (HCC)
    - No longer considered preneoplastic but rather regenerative or degenerative phenomenon
    - Low proliferation rate and absence of *p* 53 mutations also do not support preneoplastic process
- Small cell change (formerly small cell dysplasia)
  - Small hepatocytes with increased nuclear:cytoplasmic ratio and hyperchromatic nuclei
    - High proliferative activity and *p* 53 overexpression can occur
  - Likely to be preneoplastic when occurring in expansile nodules
  - Poorly defined or diffuse areas of small cell change without nodular configuration may represent regenerative phenomenon
  - Small cell regenerative foci common in biliary disease, unlikely to be preneoplastic

CLINICAL ISSUES

Presentation

- Occur in setting of cirrhosis, usually in background of hepatitis B, hepatitis C, alcoholic liver disease, hemochromatosis
  - Uncommon in chronic biliary diseases
  - Occasionally in chronic liver disease without fully developed cirrhosis
  - Can occur in noncirrhotic liver in Budd-Chiari syndrome, portal vein thrombosis, or regeneration after necrosis
- May be detected at autopsy, transplantation or by imaging
- Serum AFP is normal or mildly elevated

Treatment

- RN/LGDN: Follow-up by imaging and serological markers

- HGDN: No well-defined guidelines; often ablated

Prognosis

- RN: Most regress or remain unchanged on imaging follow-up and thus are probably not preneoplastic
  - LGDN: Unclear but low likelihood of progression
  - Difficult to ascertain prognosis, as it is difficult to clearly define LGDN
- HGDN
  - Preneoplastic lesion, likely precursor of HCC
  - Allelic imbalance in > 80% compared to 15% of RN
  - Most remain stable or regress on follow-up; progression to HCC in 10-15% based on limited studies

MACROSCOPIC

LRN (Including LGDN)

- Larger than typical cirrhotic nodules
- By definition > 1 cm but usually < 3 cm
- Pale yellow to tan or bile-stained
- Sharply circumscribed and bulge on cut section

HGDN

- Similar gross appearance as RN/LGDN
- Some HGDN are not well circumscribed and may show irregular border

MICROSCOPIC

Histologic Features

- RN
  - Resemble cirrhotic nodules; cell plates are 1-2 cells thick
    – Reticulin framework is intact

- Portal tracts are usually present within nodule, and ductular reaction may be prominent
- Occasional unpaired arterioles may be seen, but this is not prominent finding
- Hepatocytes typically appear normal; mild variation in cell size and scattered large cell change can be present

– Features for LGDN not well established

– Indistinguishable from LRN without clonality studies

- May contain Mallory-Denk bodies, bile, clear cell changes, iron, copper,

and fat
- CD34 shows patchy sinusoidal staining at edge; occasional nodules can show more diffuse expression
- Nodules are negative for α-fetoprotein and glypican-3 (GPC) with rare exceptions
- No histologic criteria to distinguish RN from LGDN

- HGDN
  - HG dysplastic changes may involve entire nodule or present as 1 or more dysplastic foci within nodule
  - By definition, atypical features do not fulfill criteria of diagnosis of HCC
  - Focal areas with up to 3-cell-thick plates may be present (normal cell plates are typically 1-2 cells thick)
    - Reticulin network is normal or focally decreased
    - Pseudoacinar architecture can be present but is usually not diffuse
  - Portal tracts are present within nodule
  - Scattered unpaired arterioles are present but not as numerous as in HCC
  - Small cell change with increased nuclear:cytoplasmic ratio is characteristic feature
    - Results in nuclear crowding and increased nuclear density
    - Large cell change can be seen but is neither sufficient nor necessary for diagnosis
  - May contain Mallory-Denk bodies, fat, clear cell change, cytoplasmic basophilia, bile
  - Tend to lack iron (in contrast to MRN, where iron deposits are more common)
  - CD34 shows patchy sinusoidal staining, usually at edge; occasional nodules can show more diffuse expression
  - α-fetoprotein is negative
  - GPC expression is variable; diffuse strong expression strongly favors HCC

DIFFERENTIAL DIAGNOSIS

Other RNs

- By definition, size > 1 cm differentiates RN from other cirrhotic nodules

Hepatic Adenoma

- Rarely, RN may lack portal zones and resemble hepatic adenoma
- True adenomas rarely, if ever, occur in cirrhotic liver

RN/LGDN vs. HGDN

- Cytologic abnormalities like small cell change and nuclear atypia favor HGDN
- Architectural abnormalities like pseudoacinar architecture, focal reticulin loss, and unpaired arterioles favor HGDN

HGDN vs. Well-Differentiated HCC

- Cell plates more than 3 cells thick are most important feature distinguishing HCC from HGDN
  - Prominent pseudoacinar architecture and numerous unpaired arterioles are typical of HCC
  - Loss or fragmentation of reticulin network strongly favors HCC
  - CD34 is typically diffuse in HCC and patchy in HGDN, but considerable overlap exists
  - CK7(+) ductular reaction present around > 50% of circumference of HGDN in most cases; this is focal or lost in most HCC
  - GPC expression favors HCC, especially if strong and diffuse
  - GPC expression described in 7-22% of HGDN also

HGDN vs. Early HCC (Early Well-Differentiated HCC or Vaguely Nodular HCC)

- Characteristic feature of early HCC is stromal invasion leading to vaguely nodular appearance
  - Stromal invasion can occur at nodule-parenchymal or nodule-septal interface within nodule or at periphery
  - Since stromal invasion can be focal, distinction from HGDN on biopsy may not be possible
  - Lack of CK7(+) ductular reaction can be useful in demonstrating stromal invasion
- Uniformly thick plates (> 3 cells), prominent pseudoglands, and loss of reticulin are typical of progressed HCC; may not be seen in early HCC
- Immunohistochemistry
  - GPC expression is more often seen in early HCC than HGDN
  - Glutamine synthetase, a downstream gene in β-catenin pathway, is diffusely positive in many early HCC (up to 70%)
    - 10-15% of HGDN can be positive (usually focal)
  - Heat shock protein 70, a cell cycle/apoptosis regulator, is overexpressed in 80% of early HCC
    - 5-10% of HGDN can be positive (usually focal)
  - When 2 of these 3 markers are positive, specificity and sensitivity for diagnosis of HCC are 100% and 72%, respectively, in resections
  - When 2 of these 3 markers are positive, specificity and sensitivity for diagnosis of HCC are 100% and 50%, respectively, in biopsies
- Most immunohistochemical stains have only been studied in limited fashion and need validation in larger studies

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

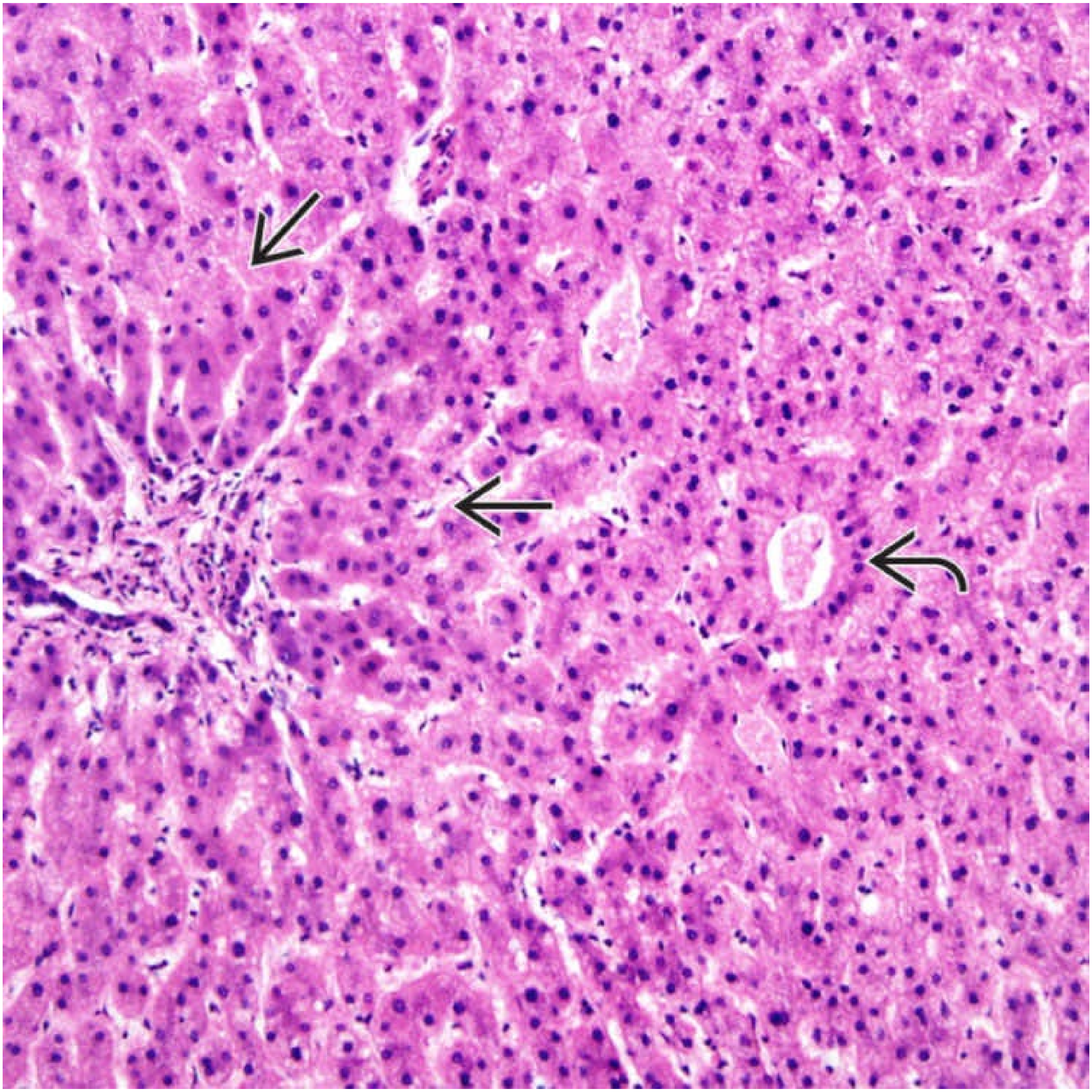
- No criteria other than clonality to distinguish LGDN from RN
  - Most RN/LGDN are probably not preneoplastic
- HGDN have significant cytologic and sometimes architectural atypia; considered precursors of HCC

Macroregenerative vs. High-Grade Dysplastic Nodule

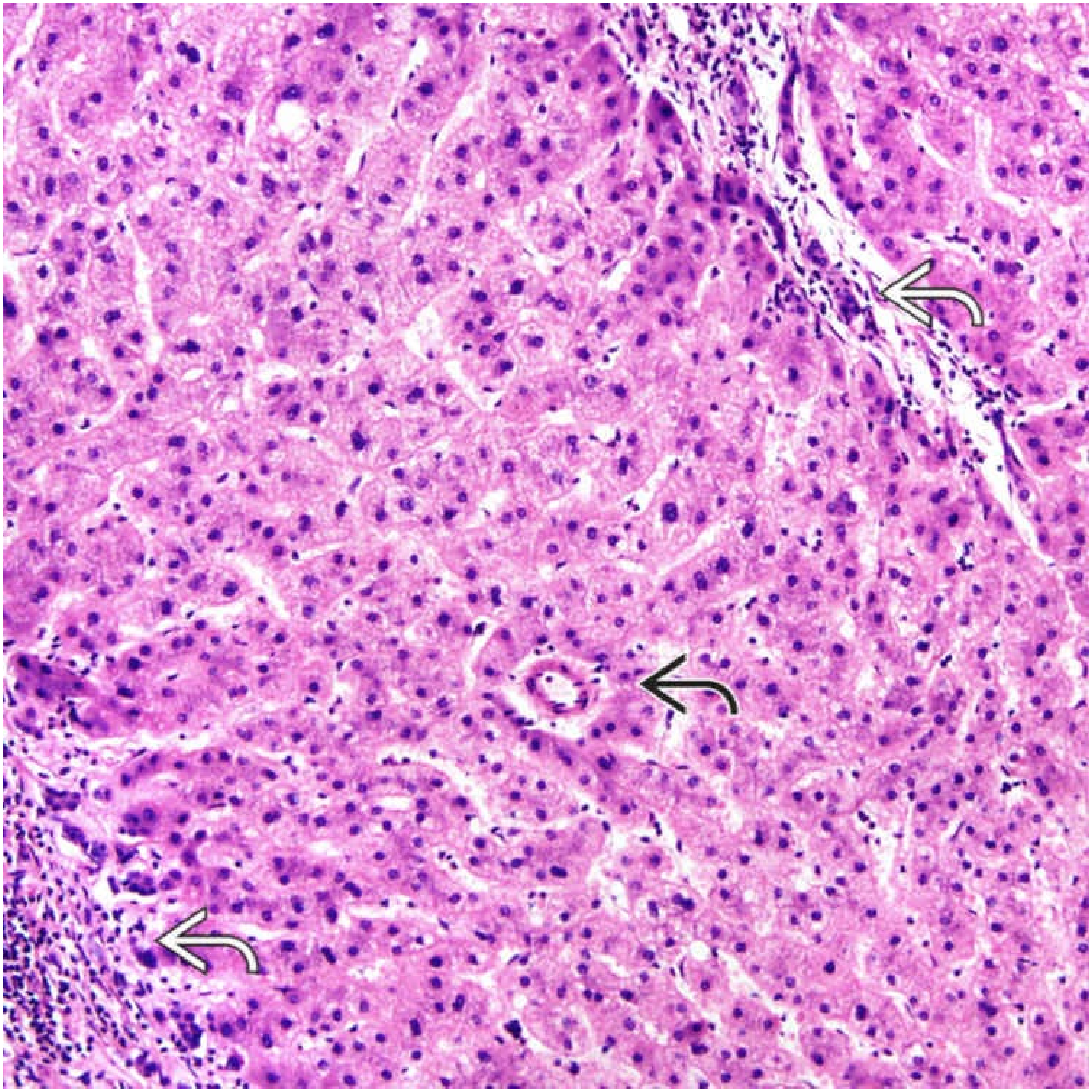
Feature	MRN	HGDN
Morphology		
Cell plate thickness	1-2	1-2, focally up to 3
Pseudoacinar architecture	Uncommon	Often present, usually not diffuse
Unpaired arterioles	Uncommon	Often present, not in large numbers
Small cell change	Absent	Characteristic
Nuclear:cytoplasmic ratio	Normal	Increased
Irregular nuclear contours	Absent	Mild
Histochemical Stains		
Reticulin network	Preserved	Preserved or focally absent
Iron	Patchy or diffuse when present, usually same as surrounding liver	Can be decreased or absent compared to surrounding liver (iron free foci)
Immunohistochemistry		
CD34 sinusoidal staining	Absent or patchy at periphery, occasionally diffuse	Patchy, occasionally diffuse
AFP	Absent	Absent
Glypican-3	Absent, rare positive cases	Absent or focal, rarely strong
CK7(+) ductular reaction	Present, diffuse	Present, may be focally lost

High-Grade Dysplastic Nodule vs. Hepatocellular Carcinoma

Feature	HGDN	Well-Differentiated HCC
Imaging		
Arterial phase	Usually hypovascular	Early HCC hypovascular, most progressed HCC hypervascular
Morphology		
Cell plate thickness	1-2, focally up to 3	> 3, can be < 3 in early cases
Pseudoacinar architecture	Usually focal	Can be diffuse
Unpaired arterioles	Present, but few	Present, often numerous
Stromal invasion	Absent	Present
Small cell change	Present	Present
Nuclear:cytoplasmic ratio	Increased	Increased
Cell density	> 1.3x normal	> 2x normal
Nuclear atypia	Mild	Mild to moderate
Cytoplasmic basophilia	Absent	Often present
Mitoses	Few or absent	Can be present
Histochemical Stains		
Reticulin	Present or focally absent	Fragmented or absent
Immunohistochemistry		
CD34	Patchy, occasionally diffuse	Usually diffuse
AFP	Negative	Can be positive
CK7(+) ductular reaction	Present or focally absent	Absent or focally present
Glypican-3	Negative or focally positive	Positive in > 50%
Glutamine synthetase	Negative or focally positive	Diffuse positive in most cases
HSP70	Usually negative or focally positive	Diffuse positive in most cases
GPC, GS, HSP70: 2 of 3 positive	None	50-60%
Serum Biochemistry		
AFP > 100 μg/mL	Less common	25-30%, L3 isoform more sensitive for early HCC

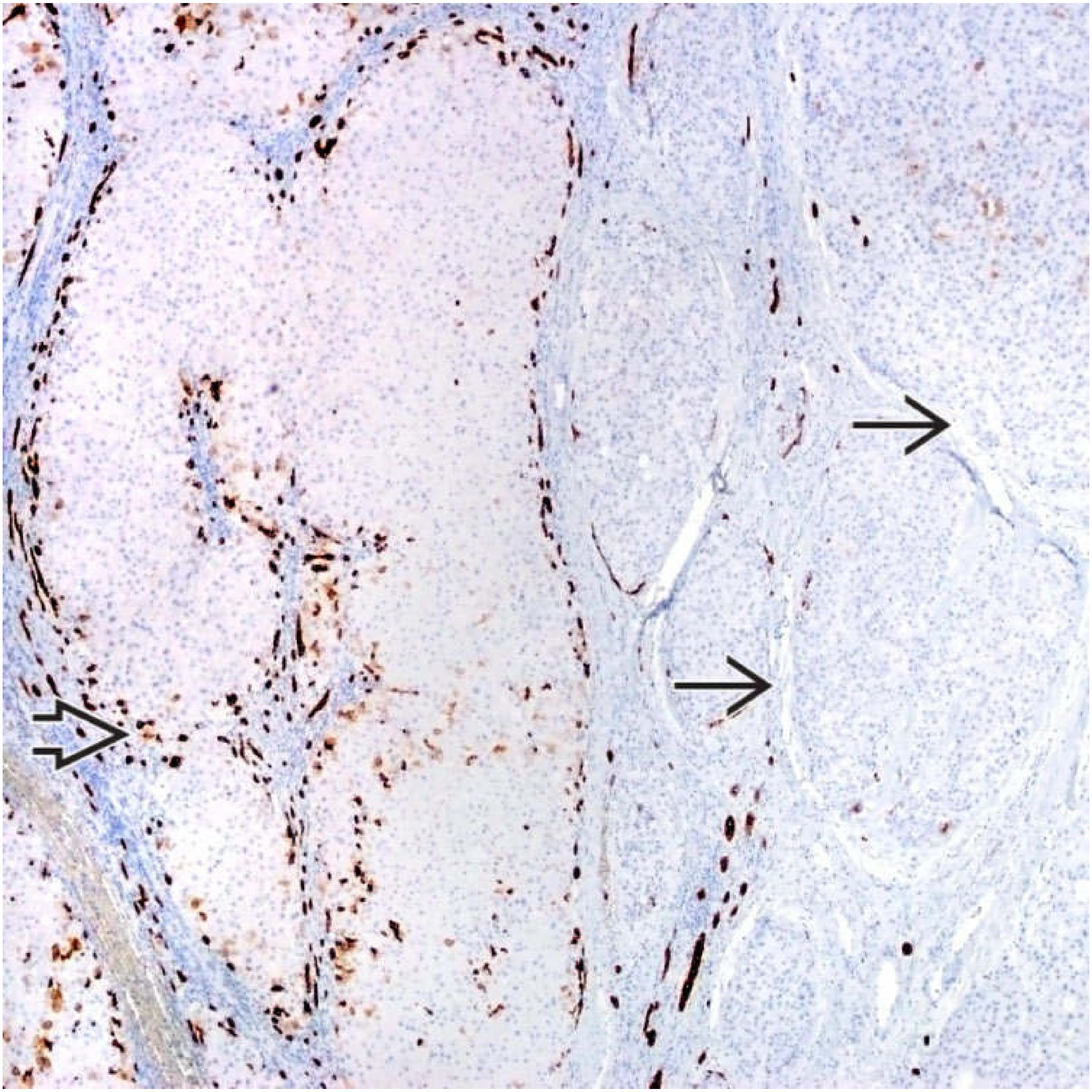


Dysplastic Nodule: Small Cell Change
Small cell change → and pseudoacinar architecture ↷ in HGDN are shown. The cytoarchitectural atypia is not prominent enough for a diagnosis of HCC.

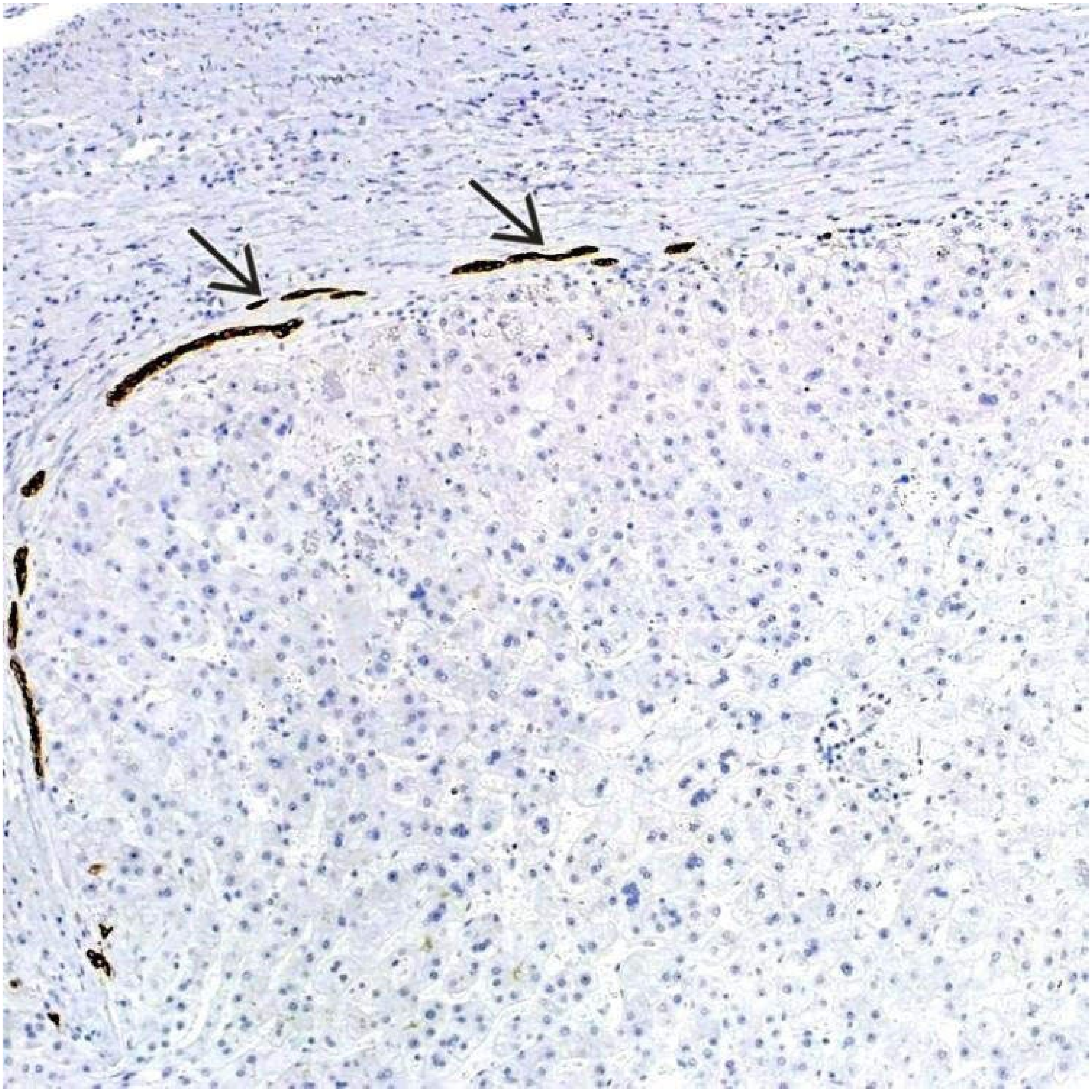


Dysplastic Nodule: Unpaired Arteriole

Unpaired arteriole is shown in an HGDN with ductular reaction within and at the periphery. Abundant unpaired arterioles and lack of ductular reaction would favor HCC.

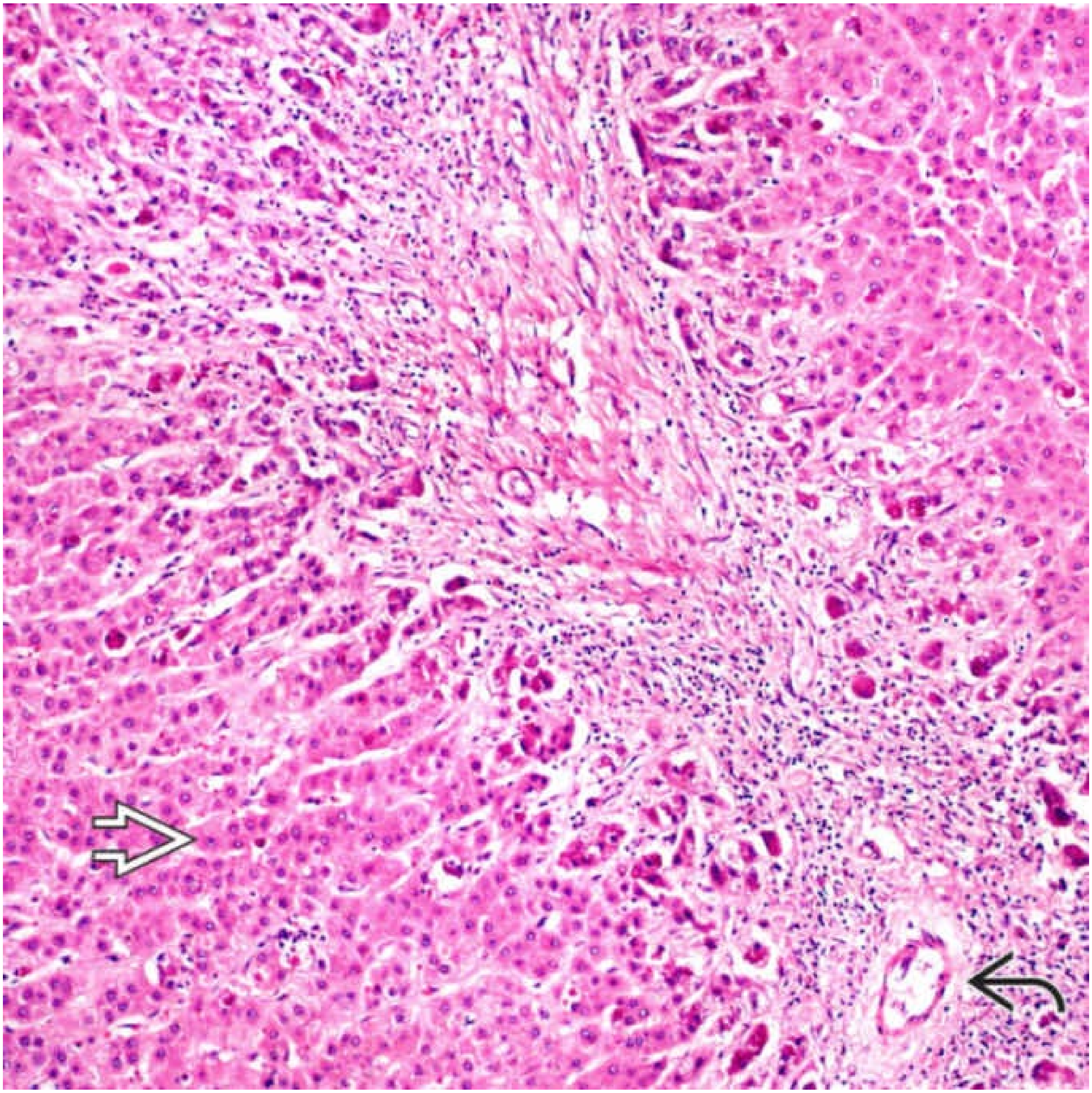


RN and HCC: CK7 Stain
CK7 immunohistochemistry highlights the circumferential ductular reaction around RNs ⇨. In contrast, the ductules are focal or absent around nodules of HCC →.

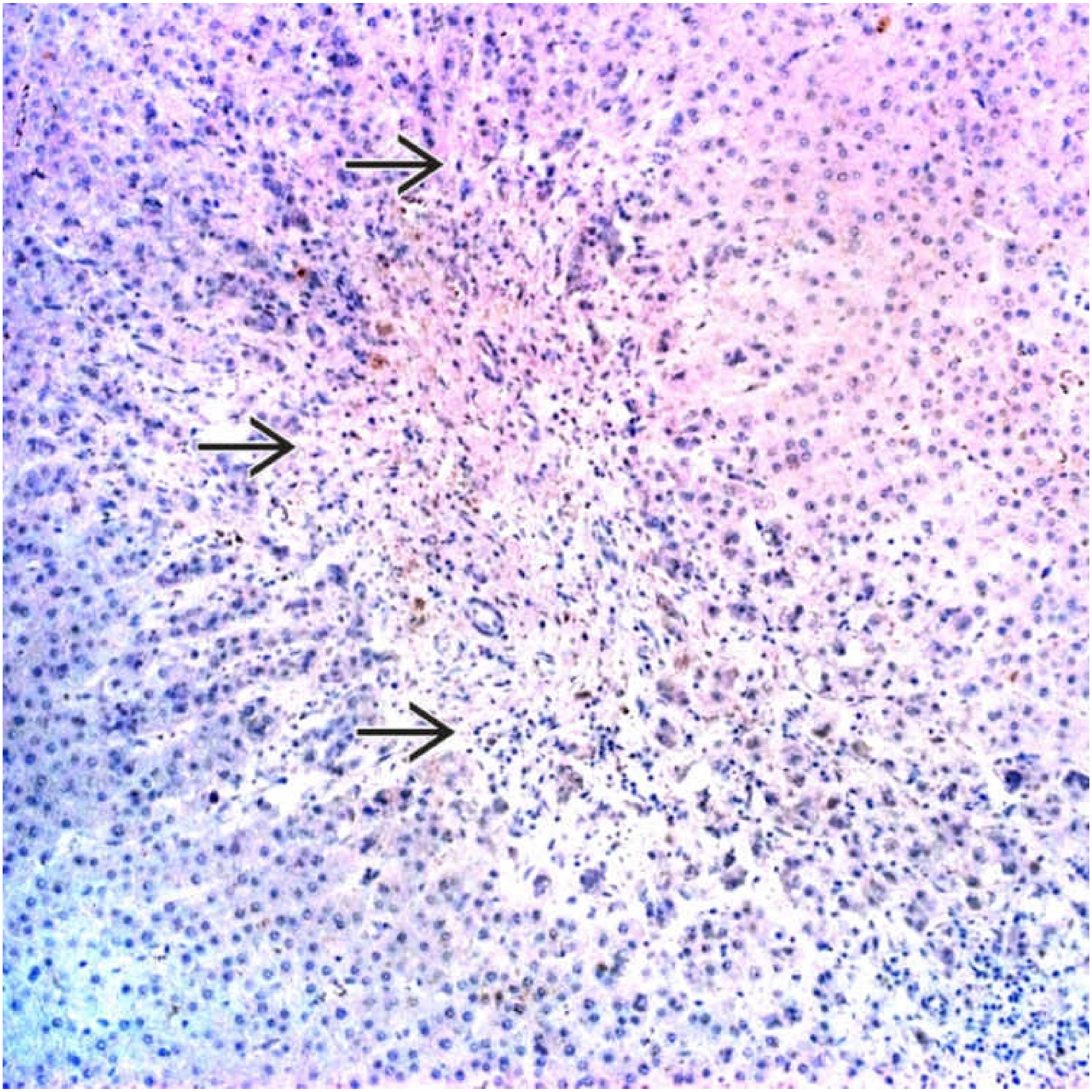


HGDN: CK7 Stain

CK7 immunohistochemistry shows a patchy ductular reaction → around a portion of the circumference of an HGDN. The finding is intermediate between RN and HCC.

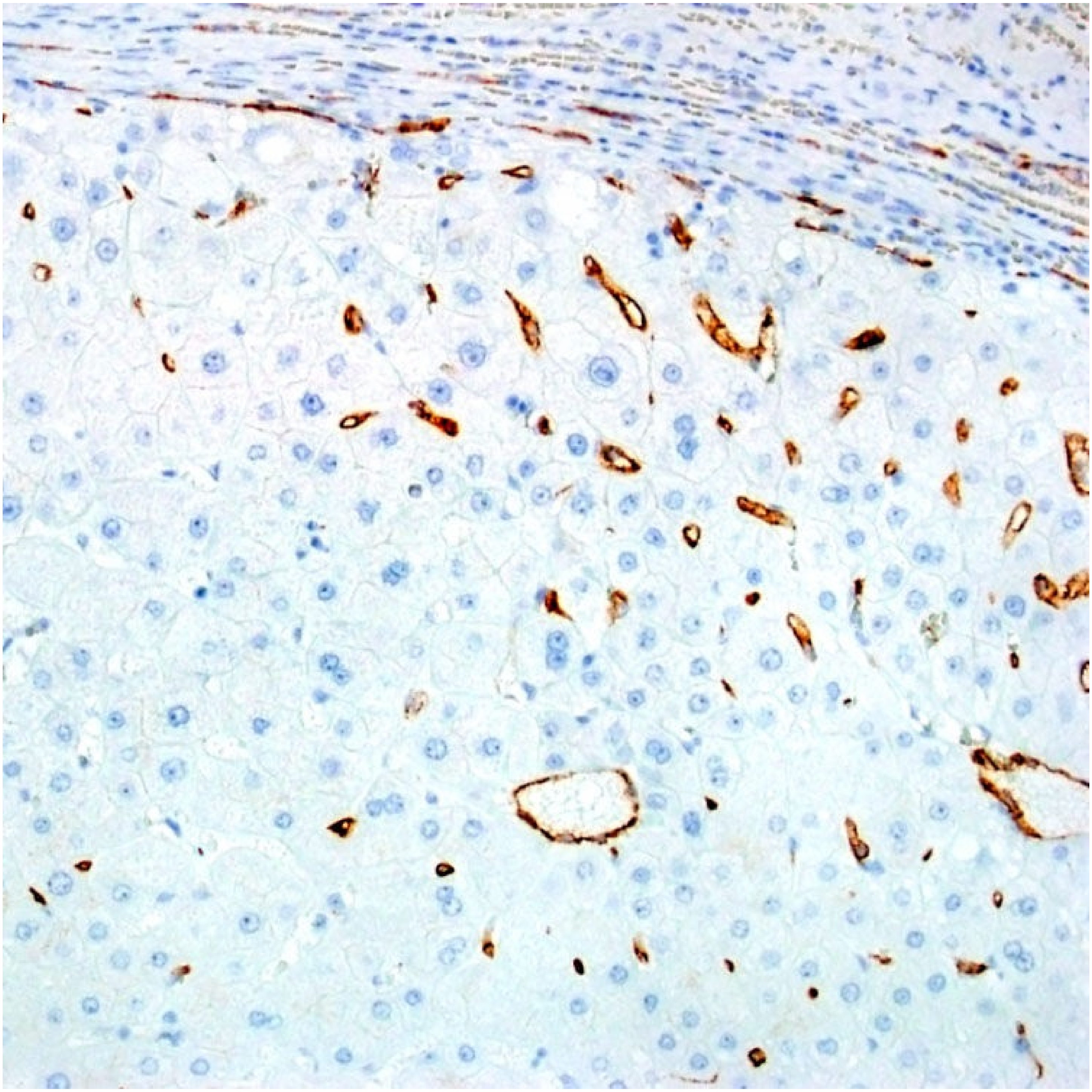


Early HCC Mimicking HGDN
H&E illustrates the intranodular hepatocellular-stromal interface in a nodule with features of HGDN, including small cell change and unpaired arterioles. The interface lacks bile ductular reaction, indicating that this is an early HCC.



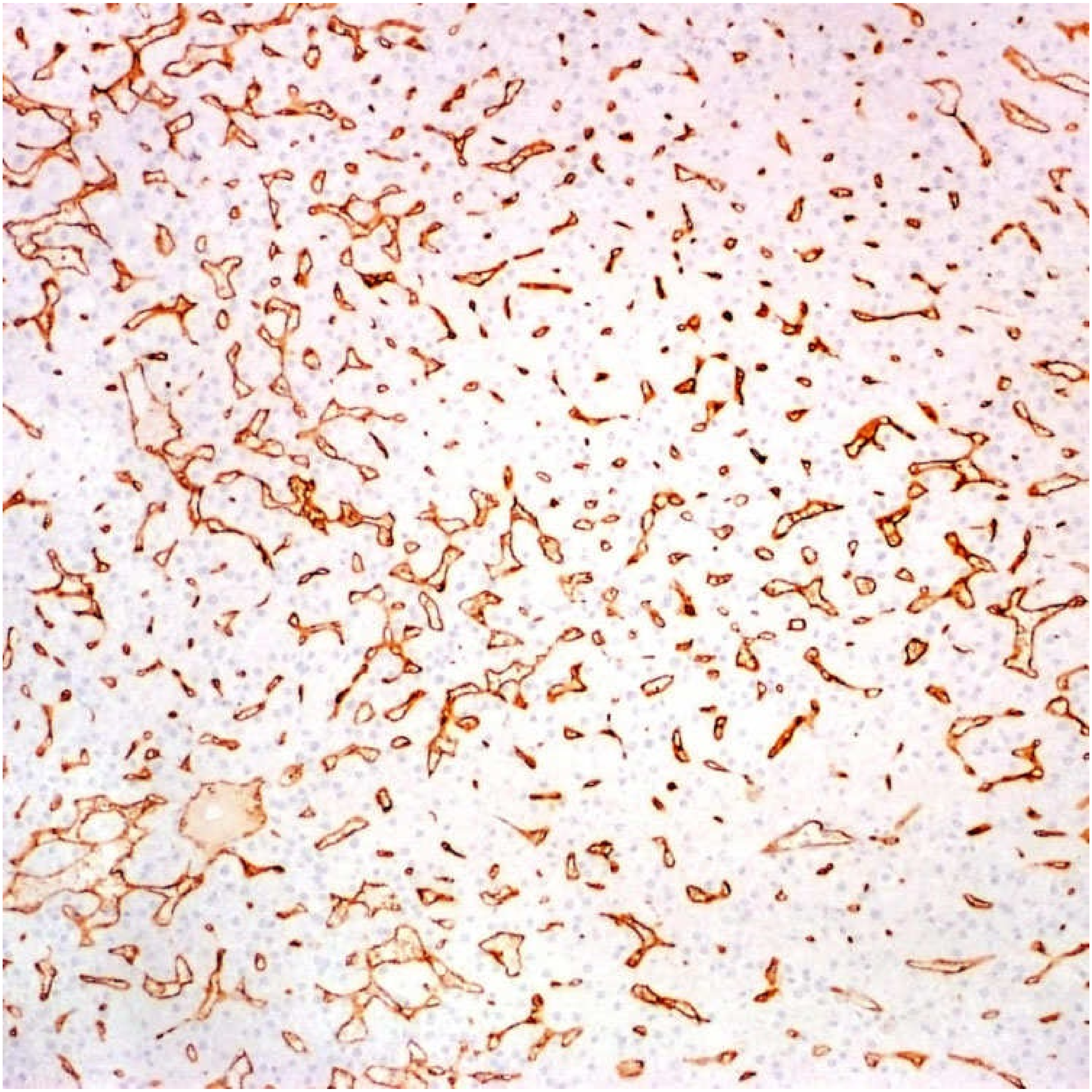
Early HCC: CK7 Stain

CK7 immunohistochemistry demonstrates a lack of ductular reaction at the intranodular hepatocellular-stromal interface →, supporting early HCC. Stromal invasion is considered to be the earliest feature of HCC.



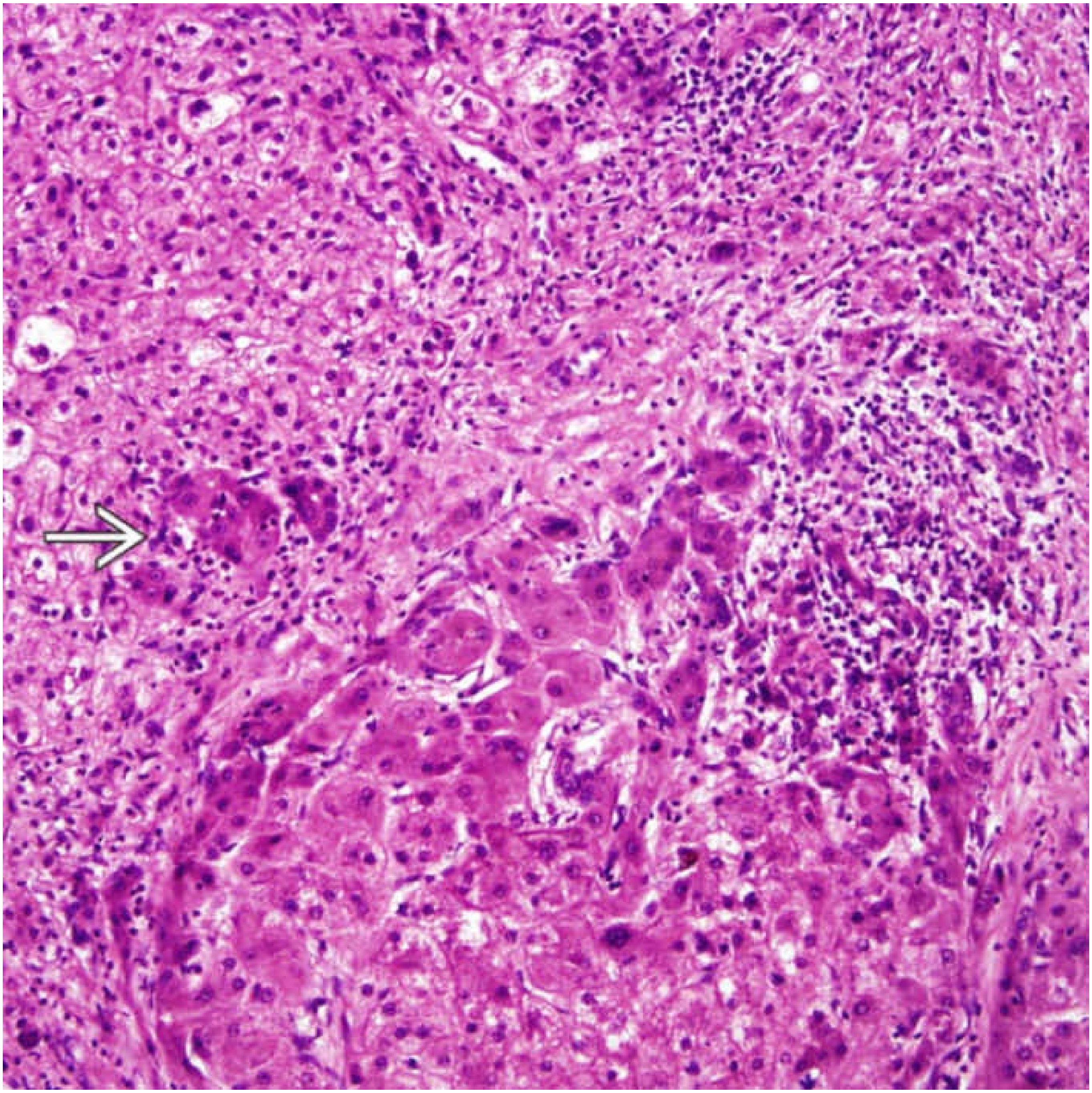
HGDN: CD34 Stain

CD34 immunohistochemistry typically shows weak and patchy sinusoidal pattern of staining in RNs and HGDNs. The patchy staining is often more pronounced at the periphery of the dysplastic nodule.



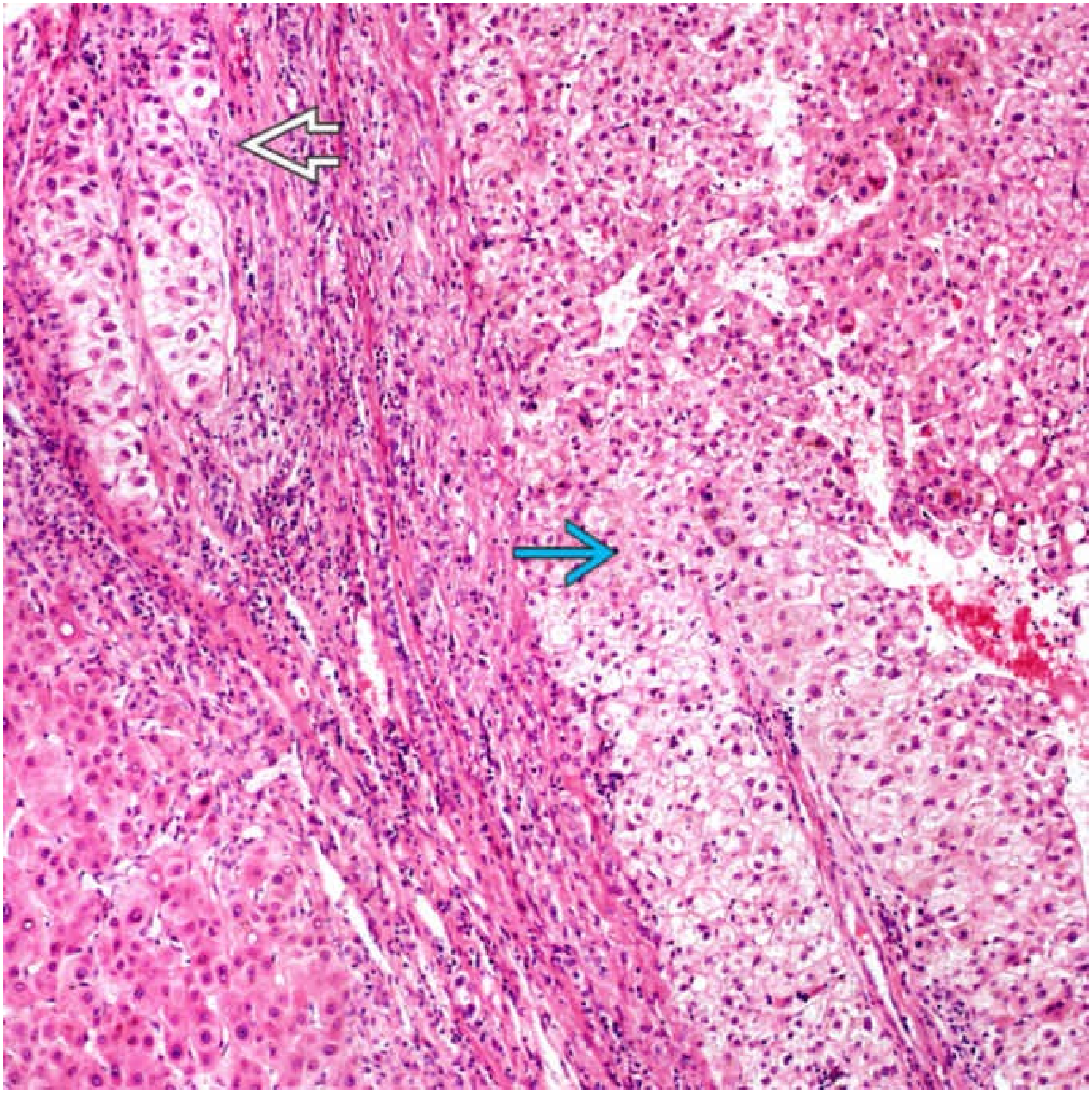
HCC: CD34 Stain

CD34 immunohistochemistry typically shows a diffuse sinusoidal pattern of staining in HCC. This staining pattern is seen in most HCC cases but may not be observed in some early cases and is not necessary for diagnosis.

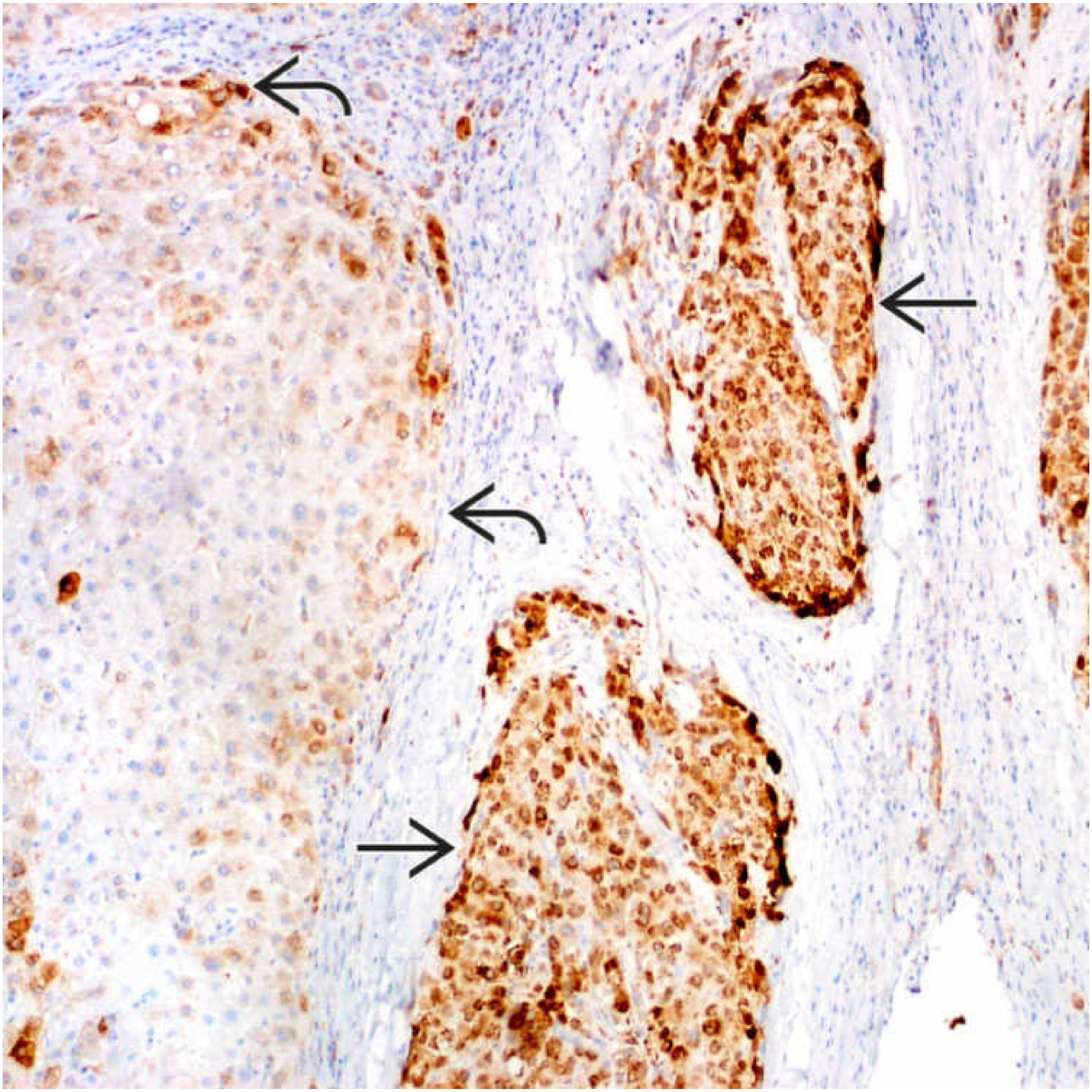


Early HCC: Stromal Invasion

This hepatocellular nodule has features of HGDN, but the infiltration of the nonneoplastic liver parenchyma at the periphery ⇒ indicates this is an early HCC. Stromal invasion is key in distinguishing early HCC from HGDN.

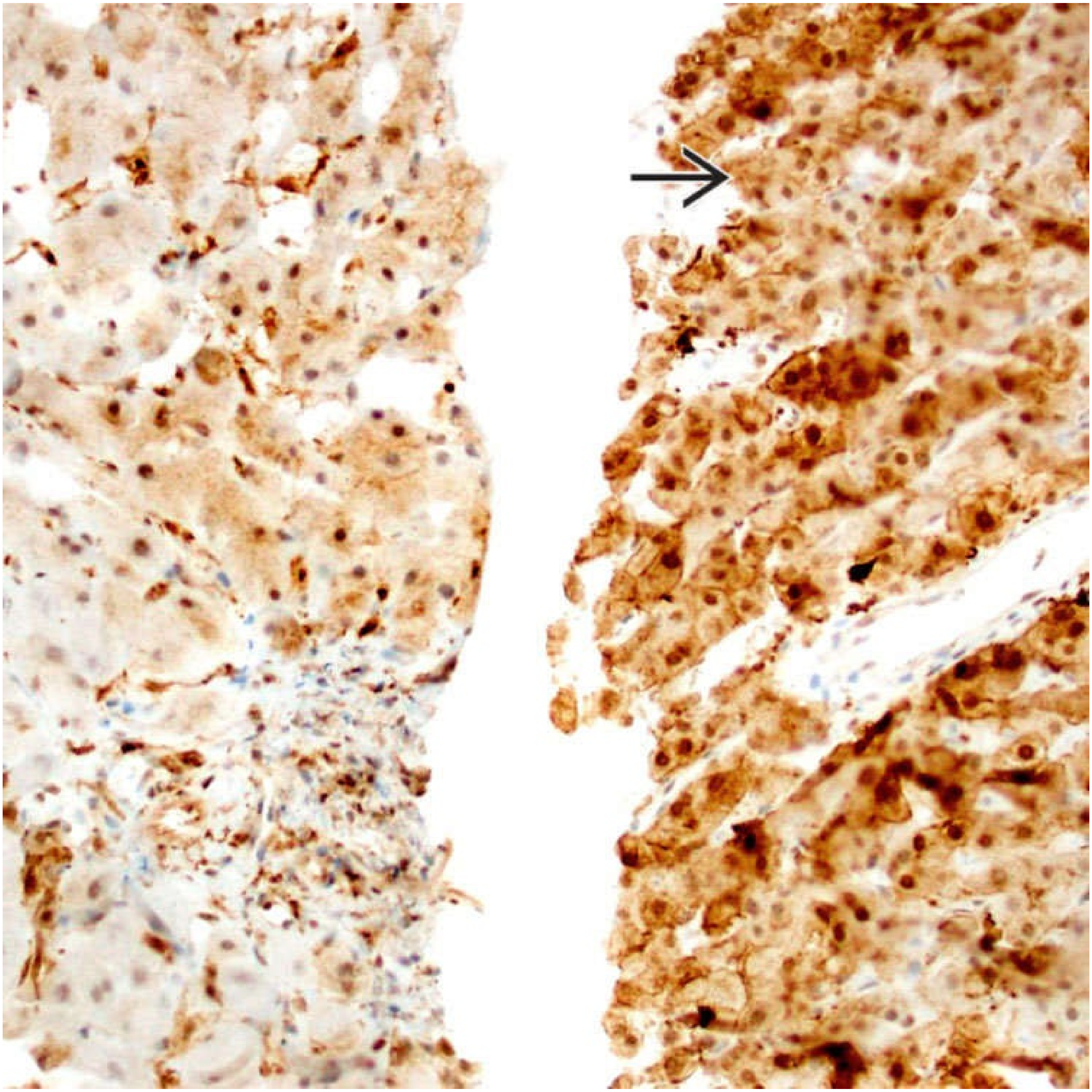


Early HCC
This hepatocellular nodule with high-grade dysplastic features → shows stromal invasion ⇨ at the periphery, supporting the diagnosis of early HCC.



HCC and HGDN: Glutamine Synthetase

Diffuse staining with glutamine synthetase is an indicator of β-catenin activation and is helpful in the distinction of HGDN and HCC. Strong cytoplasmic staining is seen in HCC → vs. the adjacent HGDN that shows patchy staining ↱ .



HCC: HSP70 Stain
HSP70 is overexpressed in HCC and can be useful in the distinction of HGDN and HCC. Note the diffuse nuclear and patchy cytoplasmic staining in early HCC →, as opposed to the adjacent cirrhotic liver that shows weak focal staining.

SELECTED REFERENCES

1. Roskams, T, et al. Pathology of early hepatocellular carcinoma: conventional and molecular diagnosis. *Semin Liver Dis*. 2010; 30(1):17–25.
2. Di Tommaso, L, et al. The application of markers (HSP70 GPC3 and GS) in liver biopsies is useful for detection of hepatocellular carcinoma. *J Hepatol*. 2009; 50(4):746–754.
3. Kondo, F. Histological features of early hepatocellular carcinomas and their developmental process: for daily practical clinical application : hepatocellular carcinoma. *Hepatol Int*. 2009;

3(1):283–293.

4. The International Consensus Group for Hepatocellular Neoplasia. Pathologic diagnosis of early hepatocellular carcinoma: a report of the International Consensus Group for Hepatocellular Neoplasia. *Hepatology*. 2009; 49(2):658–664. [Erratum in: Hepatology. 49(3):1058, 2009].
5. Shafizadeh, N, et al. Utility and limitations of glypican-3 expression for the diagnosis of hepatocellular carcinoma at both ends of the differentiation spectrum. *Mod Pathol*. 2008; 21(8):1011–1018.
6. Park, YN, et al. Ductular reaction is helpful in defining early stromal invasion, small hepatocellular carcinomas, and dysplastic nodules. *Cancer*. 2007; 109(5):915–923.
7. Sherman, M. Diagnosis of small hepatocellular carcinoma. *Hepatology*. 2005; 42(1):14–16.
8. Seki, S, et al. Outcomes of dysplastic nodules in human cirrhotic liver: a clinicopathological study. *Clin Cancer Res*. 2000; 6(9):3469–3473.
9. Lee, RG, et al. Large cell change (liver cell dysplasia) and hepatocellular carcinoma in cirrhosis: matched case-control study, pathological analysis, and pathogenetic hypothesis. *Hepatology*. 1997; 26(6):1415–1422.
10. Nakashima, O, et al. Pathomorphologic characteristics of small hepatocellular carcinoma: a special reference to small hepatocellular carcinoma with indistinct margins. *Hepatology*. 1995; 22(1):101–105.
11. Ferrell, LD, et al. Proposal for standardized criteria for the diagnosis of benign, borderline, and malignant hepatocellular lesions arising in chronic advanced liver disease. *Am J Surg Pathol*. 1993; 17(11):1113–1123.

Hepatocellular Carcinoma and Variants

KEY FACTS

Etiology/Pathogenesis

- Chronic viral hepatitis is leading cause of HCC worldwide
- 70-90% of HCC arise in cirrhosis

Clinical Issues

- α-fetoprotein is elevated in 70-90% of patients

Imaging

- Biopsy not required if findings typical of HCC
- Liver Imaging Reporting and Data System (LI-RADS) is now being used
- Combines arterial enhancement with size, venous washout, presence of capsule and growth compared to prior imaging to yield 5 diagnostic categories

Macroscopic

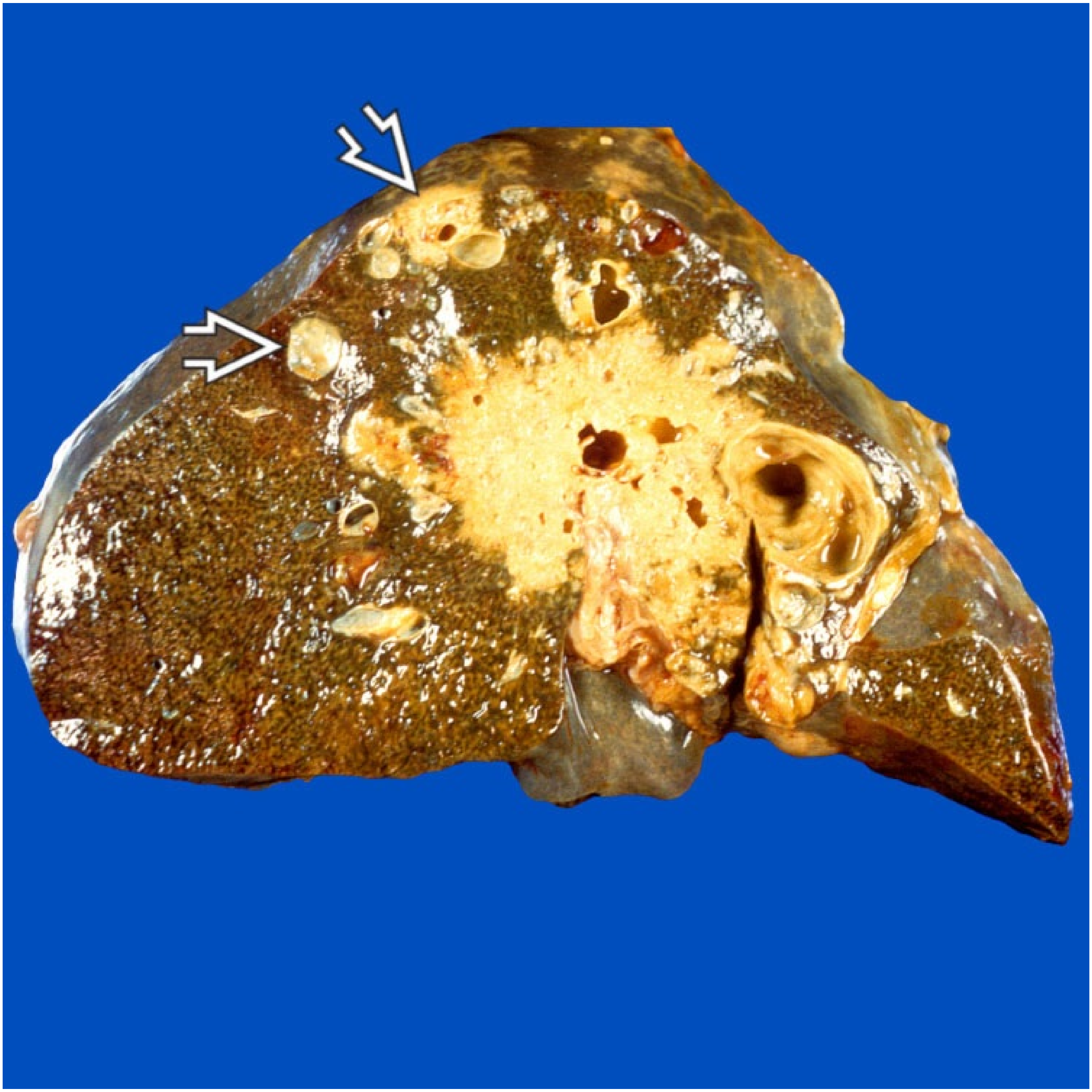
- Typically soft, bile-stained with hemorrhage and necrosis
- Can be solitary tumor, multiple discrete tumors, or small indistinct nodules throughout portion of liver

Microscopic

- Architectural patterns: Trabecular, pseudoacinar, compact
- Tumor cells resemble hepatocytes with polygonal shape, round vesicular nuclei, and prominent nucleoli
- Bile pigment in dilated canaliculi is helpful in distinguishing HCC from its mimics
- Histologic variants: Fibrolamellar, scirrhous, steatohepatitic, sarcomatoid, lymphoepithelioma-like, granulocyte-colony stimulating factor-producing HCC

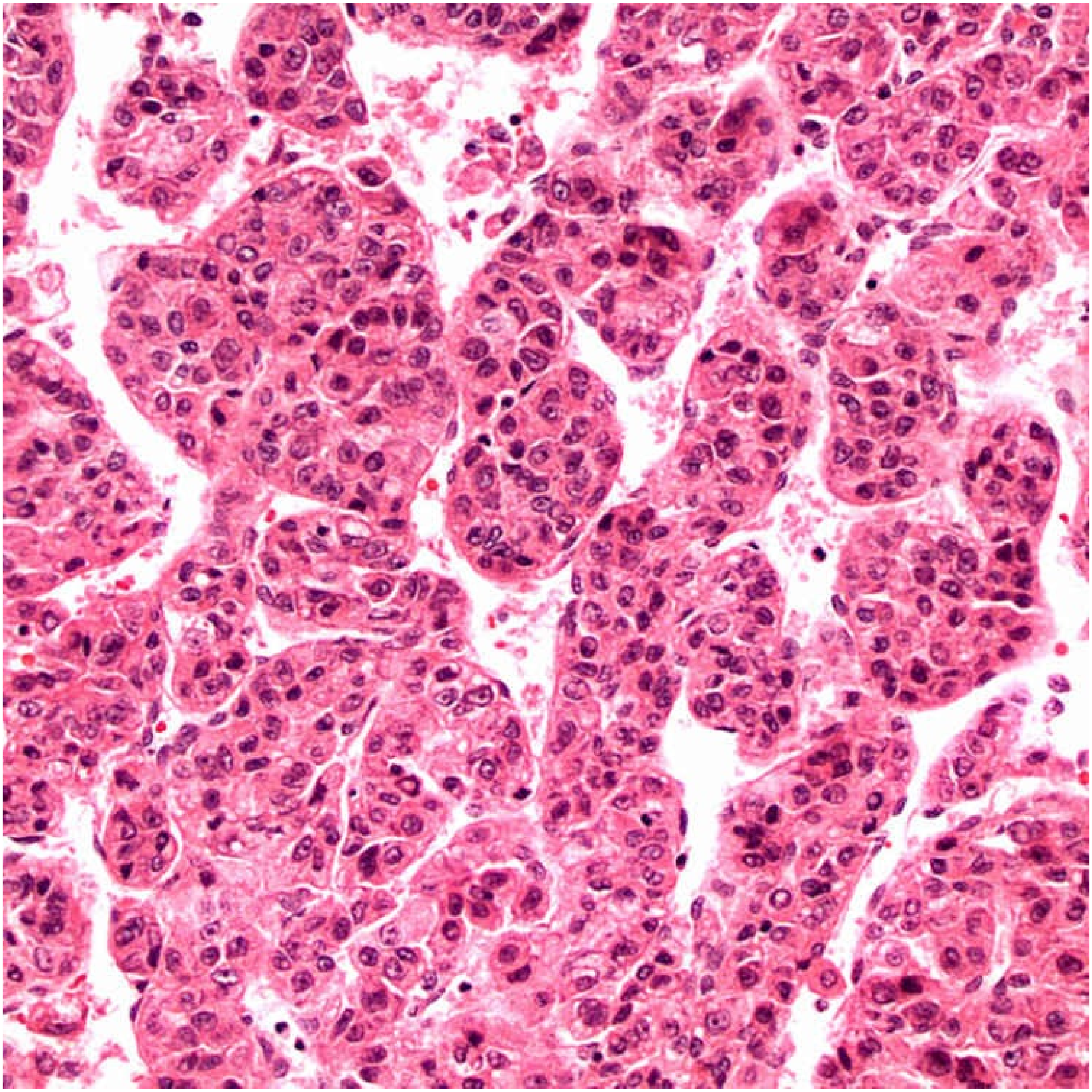
Ancillary Tests

• Arginase-1: Most sensitive and specific marker of hepatocellular differentiation
• Hep-Par1, polyclonal CEA: Overall high sensitivity, but < 50% in poorly differentiated HCC
• Glypican-3: Useful for poorly differentiated and scirrhous HCC
• Reticulin stain: Highlights widened cell plates, loss and fragmentation of reticulin framework

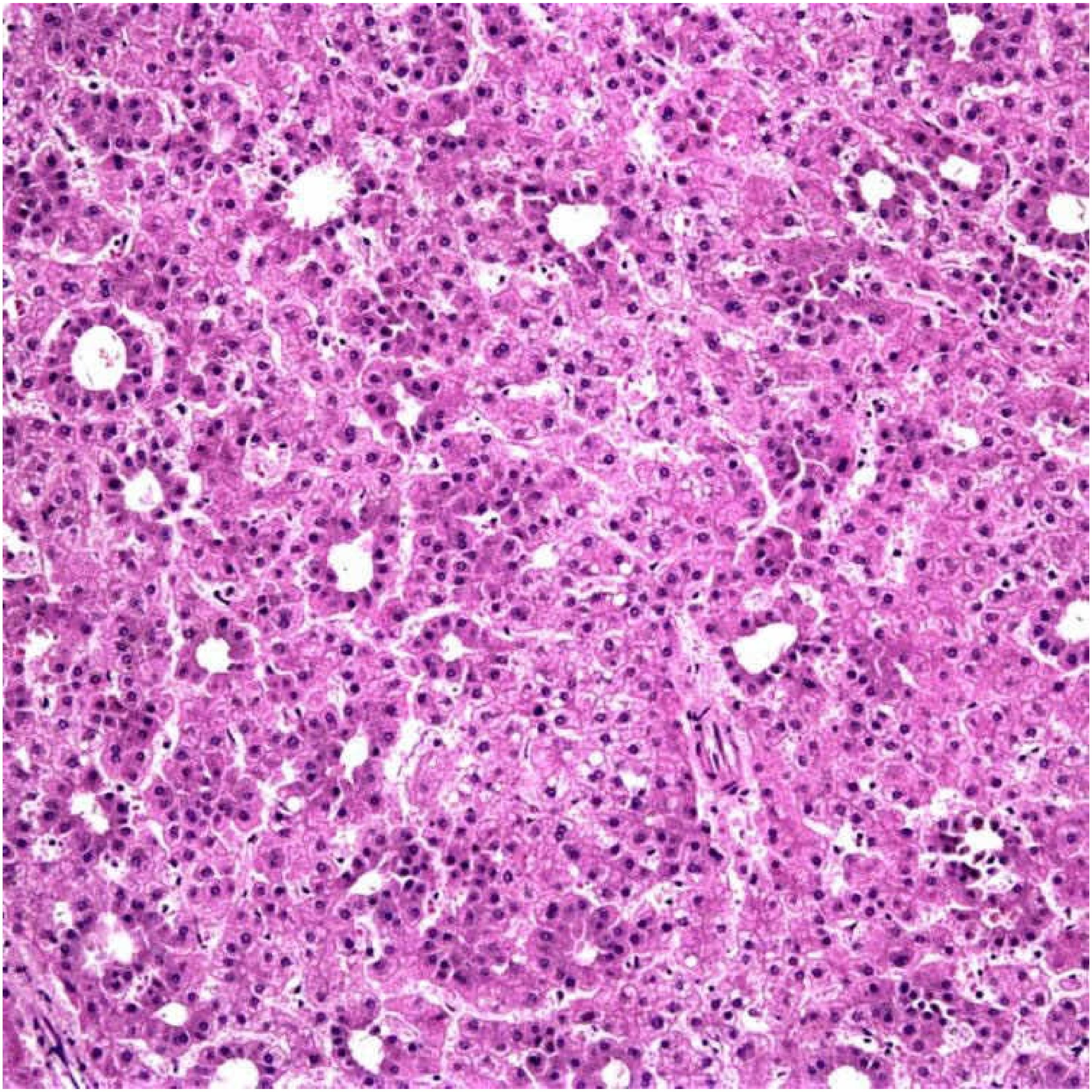


Hepatocellular Carcinoma in Cirrhotic Liver
Autopsy specimen shows a large, central mass with small satellite tumor nodules . The latter may represent intrahepatic spread due to vascular invasion or independent primaries. The nonneoplastic liver shows cirrhosis.

Hepatocellular Carcinoma in Noncirrhotic Liver
This image shows a unifocal, yellow-tan, well-circumscribed tumor in the background of a normal liver. Of hepatocellular carcinoma (HCC), 10-30% arise in noncirrhotic liver.



Trabecular Pattern
Neoplastic cells resemble hepatocytes and have a high nuclear:cytoplasmic ratio. The tumor cells are organized in thick, disordered trabeculae.



Pseudoacinar Pattern
Pseudoacinar or pseudoglandular pattern is common in HCC and can mimic adenocarcinoma. Unlike true glands, there is no basement membrane, and the nuclei do not have a basal location.

TERMINOLOGY

Abbreviations

- Hepatocellular carcinoma (HCC)

Synonyms

- Hepatoma

Definitions

- Primary malignant neoplasm of liver with hepatocytic differentiation

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- HCC can occur in patients with various congenital anomalies, including Alagille syndrome, ataxia-telangiectasia, Abernethy malformation, and genetic diseases such as bile salt export protein (BSEP) deficiency

Environmental Exposure

- Aflatoxin B1 (mycotoxin produced by fungi of *Aspergillus* genus that contaminates food) is major cause of HCC in China and southern Africa
- Alcoholic cirrhosis is major cause of HCC in western populations
- Other exposures linked to HCC include anabolic steroids, Thorotrast, oral contraceptives, and smoking

Infectious Agents

- Chronic viral hepatitis (hepatitis B and hepatitis C) is leading cause of HCC worldwide

Metabolic Disorders

- Various metabolic disorders, including hemochromatosis, tyrosinemia, hypercitrullinemia, α-1-antitrypsin deficiency, and fructosemia, are associated with increased risk of HCC
- Recent studies have implicated diabetes, obesity, and metabolic syndrome as risk factors

Cirrhosis

- 70-90% of HCC arises in cirrhosis
- Prognosis is significantly worse compared to HCC in noncirrhotic liver
- Macronodular cirrhosis is more strongly associated with HCC than micronodular

Progression of Benign Tumor

- HCC can arise in preexisting hepatocellular adenoma

CLINICAL ISSUES

Epidemiology

- Incidence
    - Varies widely depending on geography in parallel with prevalence of hepatitis B and C and aflatoxin exposure

  - East Asia and southern Africa have highest incidence worldwide, up to 150 per 100,000
  - In USA, annual incidence is ~ 4 per 100,000
- Age
  - Incidence increases with advancing age and then falls off in elderly; however, average age varies depending on geography
    - In parts of world with high incidence, average age is 35 years
    - In USA, average age is 60 years
  - Can occur in children, particularly in those with metabolic or genetic disorders
- Sex
  - More common in men

Presentation

- Abdominal pain due to stretching of Glisson capsule
- Malaise, weight loss, hepatomegaly
- Decompensation of previously stable cirrhotic patient with jaundice and rapidly accumulating ascites
- Fever, leukocytosis, and liver mass mimicking hepatic abscess
- Increasingly, small asymptomatic tumors are being found during surveillance of cirrhotic patients

Laboratory Tests

- α-fetoprotein (AFP) is elevated in 70-90% of patients

Natural History

- Metastasis occurs in 40-60% of patients
  - Most common locations are lymph nodes in porta hepatis, around pancreas, and celiac axis
- HCC has tendency for intravascular spread with involvement of hepatic and portal veins
  - Hematogenous spread most commonly occurs to lungs, but also adrenal glands, bone, stomach, heart, pancreas, kidney, spleen, and ovary
- Tumor seldom breaches Glisson capsule, and, therefore, dissemination throughout peritoneal cavity is rare

Treatment

- Surgical approaches
  - Resection is possible if sufficient reserve liver function
  - Transplantation is option if patient meets Milan criteria of single tumor < 5 cm, or < 4 tumors, none > 3 cm
  - Less stringent UCSF criteria have been proposed: Solitary tumor < 6.5 cm, or < 4 tumors, none > 4.5 cm and total tumor diameter up to 8 cm, without gross vascular invasion
  - Histologic differentiation as selection criterion has been implemented in certain centers, as poor differentiation has been shown to be associated with high recurrence
- Drugs
  - HCC is resistant to chemotherapeutic agents

- Sorafenib
  - Tyrosine kinase inhibitor that has proven to be at least somewhat effective in advanced cases
- Ablation therapy
  - Radiofrequency or microwave ablation, or direct percutaneous ethanol injections are options for small tumors
  - Transarterial embolization (TEA) and transarterial chemoembolization (TACE) can prolong survival

Prognosis

- Favorable prognostic factors
  - Age < 50 years, female gender
  - Resectable tumor
  - Noncirrhotic liver
  - Encapsulated tumor, early HCC
  - Well or moderately differentiated
  - Absence of vascular invasion
- In USA, 5-year survival is 30% for localized disease, 10% for regional disease, and < 5% for metastatic disease
- For early cancers that receive transplant, 5-year survival is 60-70%

IMAGING

Radiographic Findings

- Characteristic features on contrast-enhanced study (dynamic CT scan or MR)
  - HCC enhances more intensely than surrounding liver in arterial phase
  - HCC enhances < surrounding liver in venous phase (washout)
- Biopsy not required for diagnosis if findings typical of HCC are seen in cirrhotic liver of lesions > 2 cm
- For lesions 1-2 cm, typical radiology findings on 2 techniques increases sensitivity and specificity of diagnosis
- All suspicious lesions in noncirrhotic liver as well as ones in cirrhotic liver with atypical imaging features should be biopsied
- Liver Imaging Reporting and Data System (LI-RADS) is now being used
  - Combines arterial enhancement with size, venous washout, presence of capsule and growth compared to prior imaging to yield 5 diagnostic categories
    - LR-1: Definitely benign
    - LR-2: Probably benign
    - LR-3: Moderate probability of benign or malignant
    - LR-4: Probably malignant
    - LR-5: Definitely malignant

MACROSCOPIC

General Features

- Variable hemorrhage and necrosis, can be bile-stained
  - Solitary ± satellite nodules, or multiple discrete tumors
  - Multiple small, indistinct tumor nodules can mimic cirrhosis on imaging and gross examination (cirrhosis-like variant)
  - Pedunculated tumors are rare, more easily resected and have better prognosis
  - Encapsulated tumors are usually solitary tumors that arise in cirrhotic livers and have better prognosis
- Gross venous or bile duct invasion may be seen

MICROSCOPIC

Histologic Features

- Architectural patterns
  - Trabecular pattern: Tumor cells grow as thickened hepatic plates separated by sinusoids without desmoplastic stroma
  - Pseudoglandular or acinar pattern: Tumor cells grow in solid nests with central degenerative changes
  - Compact pattern: Trabeculae grow compressed together
  - Spindle cell pattern: Often referred to as sarcomatoid HCC
- Tumor cell morphology
  - Tumor cells resemble hepatocytes with polygonal shape, round vesicular nuclei, and prominent nucleoli
  - Inclusions can be seen in tumor cells: Mallory hyaline, ground-glass inclusions, hyaline globules, pale bodies
  - Clear cells may be present and even numerous due to accumulation of glycogen or fat
  - Bizarre mono- or multinucleate tumor giant cells, rarely osteoclast-like giant cells
  - Cytoplasmic fat can be present, often diffuse in small, well-differentiated tumors
  - Bile can be present in dilated canaliculi, helpful in distinguishing HCC from its mimics

Cytologic Features

- Neoplastic cells resemble hepatocytes but with enlarged nuclei, nuclear membrane irregularity, coarse chromatin, and prominent macronucleoli
  - May have dispersed cell pattern with numerous stripped, atypical nuclei
- Tumor cells tend to be more monotonous with less anisonucleosis and higher nuclear:cytoplasmic ratio than benign hepatocytes
- Thick, disordered plates or balls of neoplastic cells, focally lined by sinusoidal endothelial cells (endothelial wrapping)
- Large tissue fragments traversed by blood vessels

Fibrolamellar Carcinoma

- 5% of hepatocellular carcinomas
  - Arises in noncirrhotic livers
  - Affects both sexes equally, usually < 35 years of age
  - 5-year survival rate of ~ 50%
  - Better prognosis than conventional HCC arising in cirrhosis, but overall survival similar to

conventional HCC in noncirrhotic liver

- Gross examination: Lobulated appearance with fibrous septa or central stellate scar
- Triad of morphologic features: All 3 should be present for making diagnosis
  - Nests and sheets of large polygonal tumor cells with vesicular nuclei and single prominent nucleoli
  - Abundant granular eosinophilic (oncocytic) cytoplasm
  - Fibrous stroma composed of parallel lamellae of collagen
- Pale bodies are present more often than conventional HCC
- Focal glandular differentiation and focal staining for neuroendocrine markers can be seen
- CK7 and CD68 are typically positive
- Characteristic, recently described 400 bp deletion on chromosome 19 in 80-90% of cases
  - Leads to novel *PRKACA-DNAJB1* fusion transcript that encodes a chimeric protein with full retention of protein kinase A activity
  - Can be detected in paraffin-embedded tissue by reverse transcription polymerase chain reaction (RT-PCR) or break-apart FISH probe
  - Specificity for fibrolamellar carcinoma needs to be confirmed

Scirrhous Hepatocellular Carcinoma

- Definition of > 50% fibrous stroma arbitrarily used to define this variant in most studies
- Hep-Par1, polyclonal CEA often negative
- CK7, CK19, &/or MOC31 often positive
- Morphology and immunoprofile can be mistaken for cholangiocarcinoma or metastatic adenocarcinoma
- Arginase-1 and glypican-3 have higher sensitivity compared to other hepatocellular markers for diagnosis of this variant

Steatohepatitic Hepatocellular Carcinoma

- HCC with tumor cells showing steatohepatitic changes: Steatosis, ballooning, Mallory hyaline
- Strongly associated with steatohepatitis and metabolic syndrome
- Less commonly described in other liver diseases such as chronic hepatitis C

Sarcomatoid Hepatocellular Carcinoma

- Partly or completely composed of malignant spindle cells
- Hepatocellular markers typically negative in spindle cells; identification of typical HCC component necessary to make diagnosis
- Keratin usually positive: Use of multiple antibodies like AE1/AE3, CAM5.2, MNF116 increases sensitivity
- Heterologous differentiation can occur (smooth muscle, skeletal muscle, bone/cartilage, etc.)
- Sarcomatoid change can occur following chemotherapy or transarterial chemoembolization
- More aggressive than conventional HCC based on limited data

Lymphoepithelioma-Like Carcinoma

- Rare variant with syncytial growth pattern and abundant lymphocytes similar to nasopharyngeal

carcinoma
- EBV often positive
- Most cases are microsatellite stable

Granulocyte-Colony Stimulating Factor-Producing Hepatocellular Carcinoma

- Rare variant with production of G-CSF by tumor cells
- Leukocytosis &/or abundant neutrophilic infiltration amidst tumor cells
- Abundant neutrophils also occur in HCC with overexpression of CXCL5 (epithelial neutrophil-activating peptide-78)

Hepatocellular Carcinoma With Stem Cell Features

- Not recognized variant in WHO 2010 classification
- Small, uniform tumor cells at periphery of nests and trabeculae typical of HCC, and may also form nests and trabeculae of their own
- More common in scirrhous variant of HCC
- Small tumor cells thought to be stem cells, may be negative for hepatocellular markers like Hep-Par1 and arginase-1
- AFP and glypican-3 can be positive
- Variable staining reported with CK19, CD56, KIT, CD133, none of which are specific for stem cells
- May be more aggressive, but detailed outcome studies are not available

ANCILLARY TESTS

Histochemistry

- Reticulin stain
  - Highlights widened cell plates
  - Loss and fragmentation of reticulin framework
  - May be intact in very well-differentiated cases
  - Not reliable in presence of fat as nonneoplastic liver with steatosis also shows reticulin fragmentation

Immunohistochemistry

- Hepatocellular markers
  - Arginase-1: Most sensitive and specific marker of hepatocellular differentiation
  - Hep-Par1: Overall high sensitivity, but < 50% in poorly differentiated HCC
    – Some adenocarcinomas and neuroendocrine carcinomas can show positive staining
  - Glypican-3: Not specific hepatocellular marker
    – High sensitivity for poorly differentiated and scirrhous HCC
    – Low sensitivity in well-differentiated cases

– Negative in benign lesions like adenoma

- Polyclonal CEA and CD10 demonstrate canalicular pattern, limited sensitivity in poorly differentiated HCC
- AFP staining has high specificity but low sensitivity (20-30%) and often shows background staining

- Sinusoidal capillarization demonstrated with CD34
- Keratin
  - Pankeratin, CAM5.2 (keratins 8 and 18): Positive
  - CK7, CK19: Positive in 5-20% of cases, CK19 staining is associated with poor prognosis
  - CK20: Negative or focal; diffuse staining in rare cases

DIFFERENTIAL DIAGNOSIS

Cholangiocarcinoma

- Discrete gland formation
- Desmoplastic stroma
- Mucicarmine (+); positive for CK7, CK19, MOC-31, &/or CA19-9

Metastatic Neuroendocrine Tumor

- Prominent collagenous stroma
- Positive staining for neuroendocrine markers
- Hepatocellular markers negative; rare cases can show aberrant staining with Hep-Par1

Metastatic Adenocarcinoma

- Mucicarmine (+); MOC-31(+), keratin profile not limited to 8 and 18

Angiomyolipoma

- Adipose tissue and muscular arteries; may not be present in monotypic variant
- Myoid component can be spindle or epithelioid
- HMB-45(+), smooth muscle actin (+), Arginase-1 (-), Hep-Par1(-)
- Keratin (-)

Metastatic Renal Cell Carcinoma

- History of renal cell carcinoma or renal tumor, no cirrhosis
- Arginase-1 (-), Hep-Par1(-), pax-2(+), pax-8(+)

Hepatocellular Adenoma

- Female gender

- No or minimal cytologic atypia, 1-2 cell thick plates, intact reticulin network
- Glypican-3 and HSP70 typically negative

Regenerative Nodule in Cirrhosis

- Cytologically benign; absence of trabecular or pseudoglandular growth pattern
- Portal tracts present in nodule
- Intact reticulin

Dysplastic Nodule in Cirrhosis

- Small cell change &/or focally wide cell plates
- May have portal tracts, few unpaired arterioles
- Ductular reaction at stromal interface, lacks invasion of intranodular portal tracts or adjacent liver
- Reticulin intact or focal loss
- Stromal invasion and immunohistochemistry for glutamine synthetase, HSP70, and glypican-3 may help in distinction from early HCC

Combined Hepatocellular-Cholangiocarcinoma

- Additional cholangiocarcinoma component defined by discrete gland formation
  - Mucin helpful to confirm cholangiocarcinoma component, but is not always present
  - Strong staining for CK7, CK19, &/or MOC31 in cholangiocarcinoma component
  - Since these markers can be positive in HCC as well, these should not be used in absence of corresponding morphologic features
- Strict criteria for diagnosis should be used due to significant therapeutic implications
  - Cholangiocarcinoma component increases chances of lymph node involvement, which may require lymph node dissection for resectable tumors
  - Gemcitabine-based chemotherapy may be used if cholangiocarcinoma component is present
  - Cholangiocarcinoma may exclude option of liver transplantation

Metastatic Adrenocortical Carcinoma

- Pankeratin weak or absent; hepatocellular markers negative
- Positive for inhibin, calretinin, &/or Melan-A

Hepatoid Carcinoma

- Rare extrahepatic tumor that resembles HCC on morphology and immunohistochemistry
- Solid/hepatoid pattern, often with tubular component
- Serum AFP can be elevated
- Primary sites: Stomach, pancreas, gallbladder, colon, lung, urinary bladder
- Hepatocellular markers including arginase-1, AFP, and glypican-3 can be positive
- CK19 and CK20 can be positive
- SALL4, transcription factor used in diagnosis of germ cell tumors, can be positive
- Aggressive tumors with poor outcome

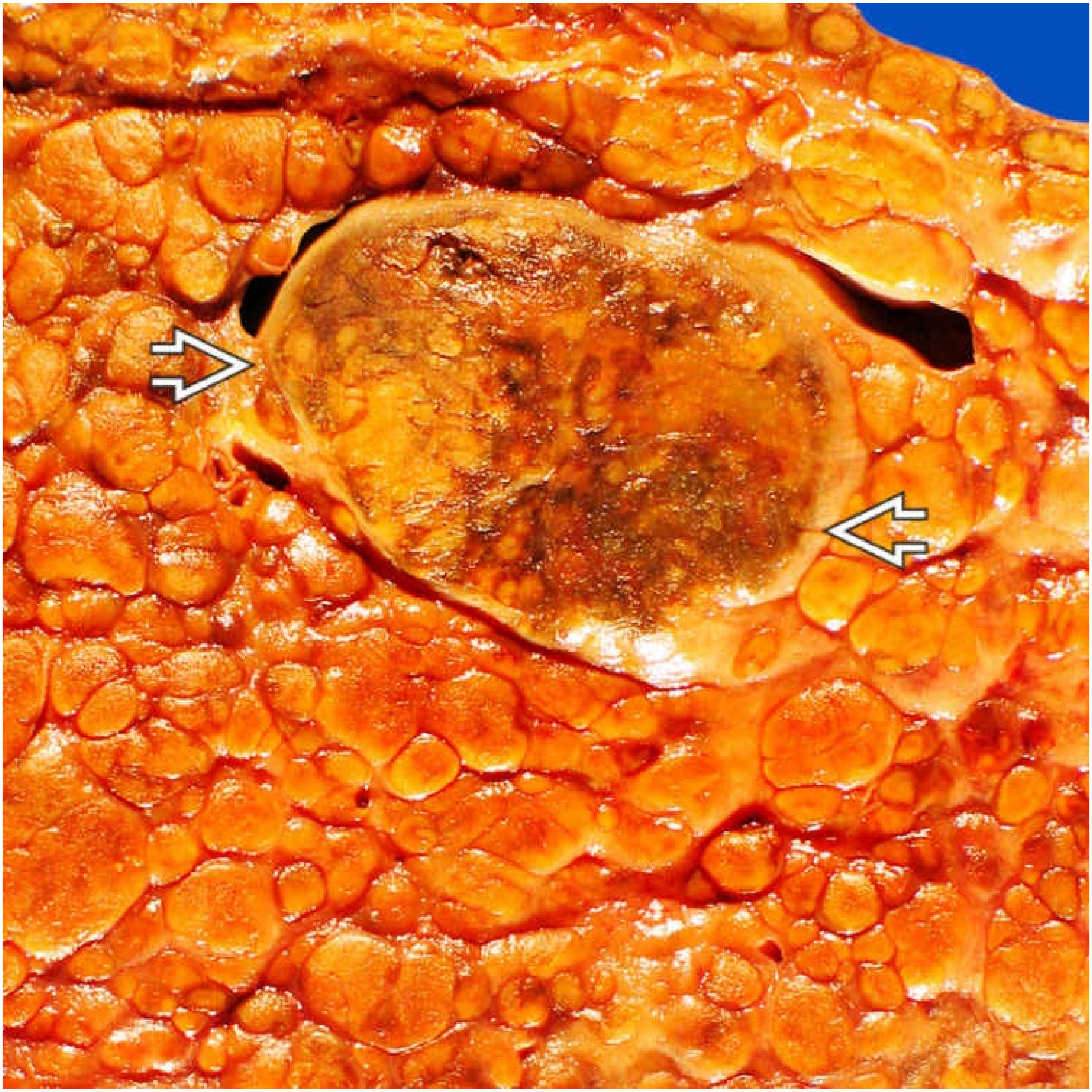
GRADING

Edmondson and Steiner

- Grade I: Extremely well-differentiated; challenging to distinguish from adenoma or dysplastic nodule; mild nuclear enlargement; pseudoacini may be present
- Grade II: Resemblance to hepatocytes; nuclei larger and more hyperchromatic than normal; low N:C ratio; pseudoacini often frequent
- Grade III: Nuclei larger and more hyperchromatic than grade 2 tumors; higher N:C ratio; break-up or distortion of trabecular pattern; tumor giant cells can be present
- Grade IV: Nuclei intensely hyperchromatic; high N:C ratio with often scanty cytoplasm; indistinct trabeculae; loosely cohesive cell nests; spindle cell areas can be present

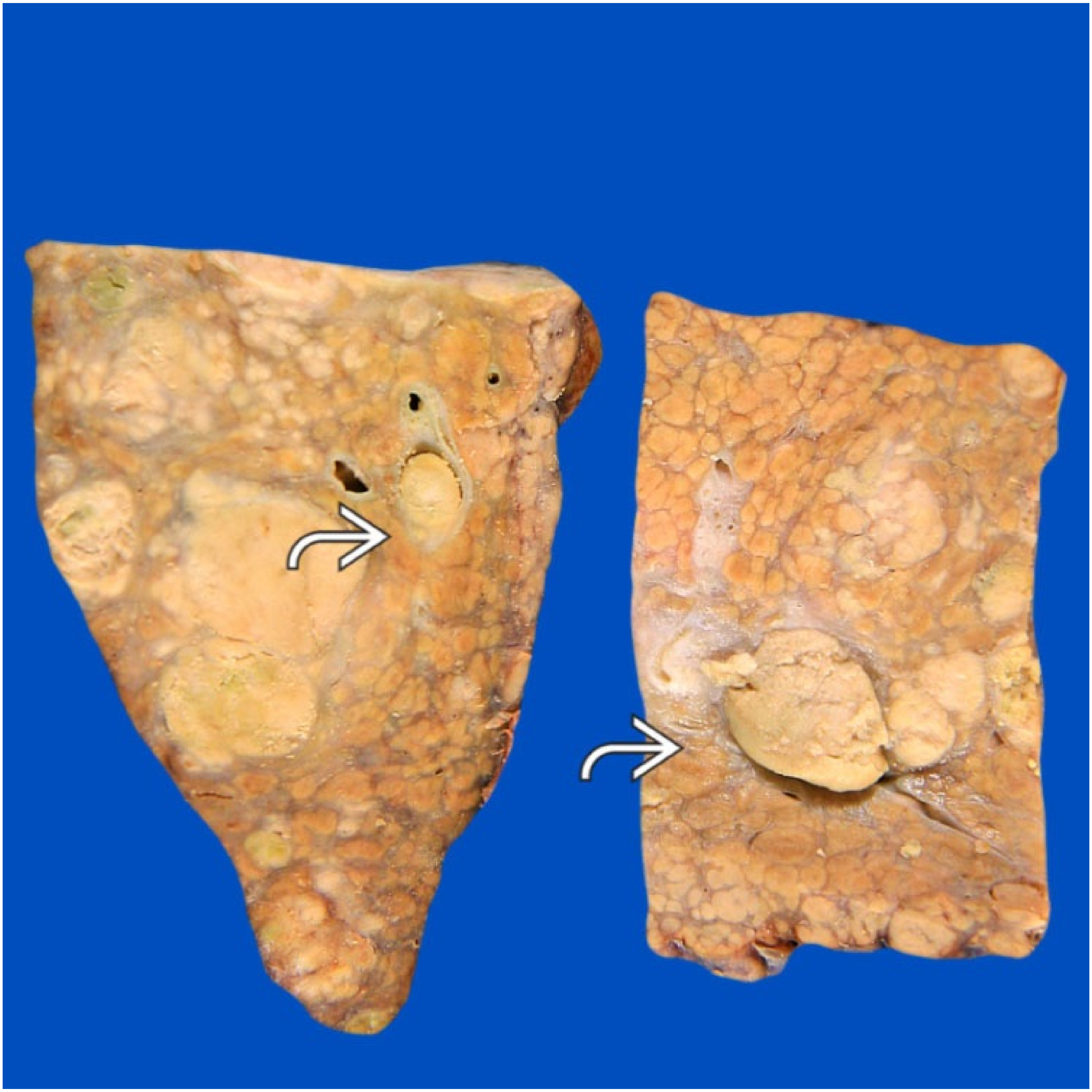
WHO 2010

- Well differentiated: Mild atypia; increased N:C ratio; pseudoacini and steatosis are common
- Moderately differentiated: Tumor cells resembling hepatocytes arranged in trabeculae of ≥ 3 cells in thickness; abundant cytoplasm, round nuclei, and distinct nucleoli; pseudoacini with bile can be present
- Poorly differentiated: Solid pattern without distinct sinusoid-like spaces; high N:C ratio; moderate to marked pleomorphism
- Undifferentiated: Solid pattern, spindle or round tumor cells, little cytoplasm

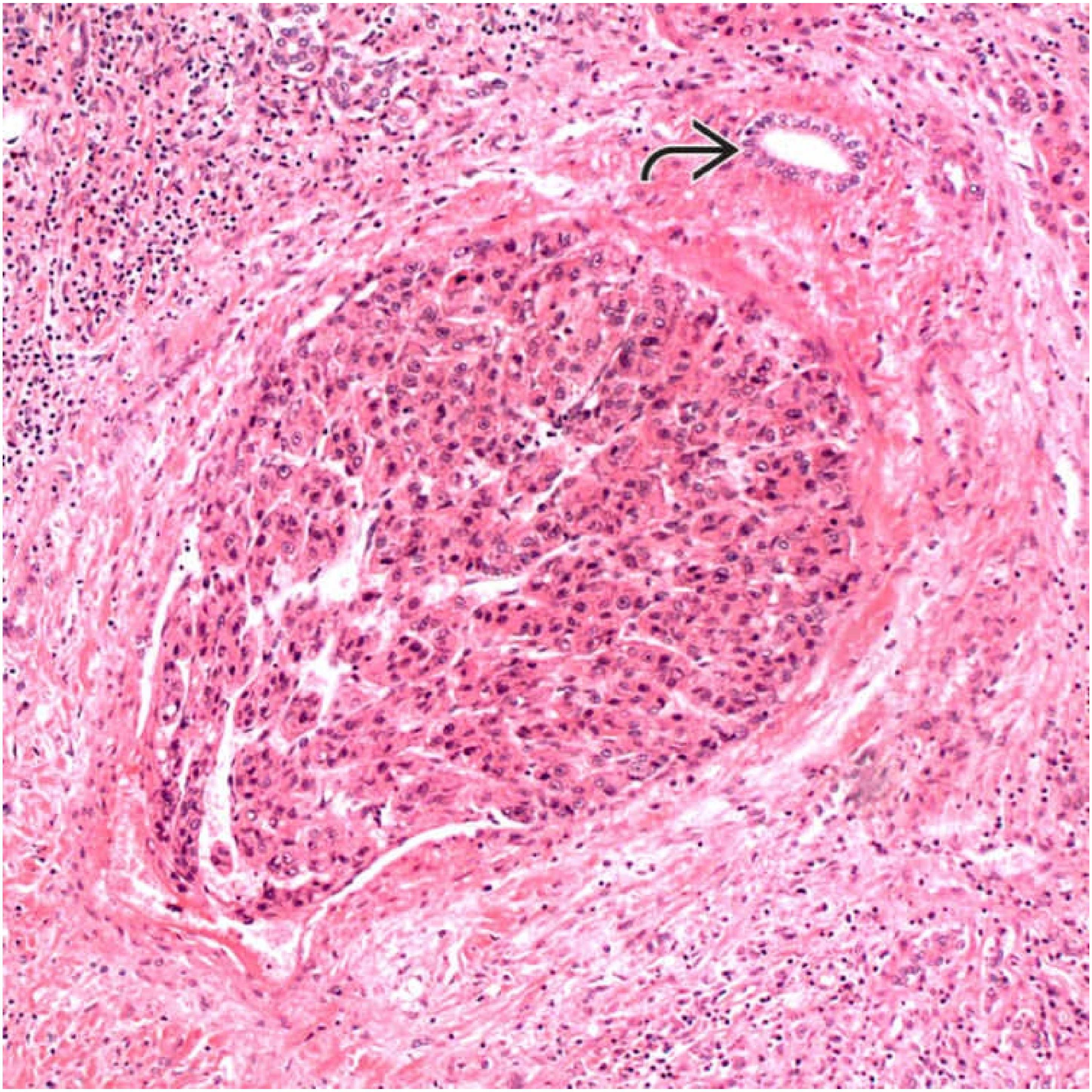


Hepatocellular Carcinoma
This image shows a large, bile-stained tumor nodule ⇨ in this cirrhotic liver.

Multifocal Hepatocellular Carcinoma
This image shows multiple nodules of hepatocellular carcinoma arising in a background of cirrhosis.

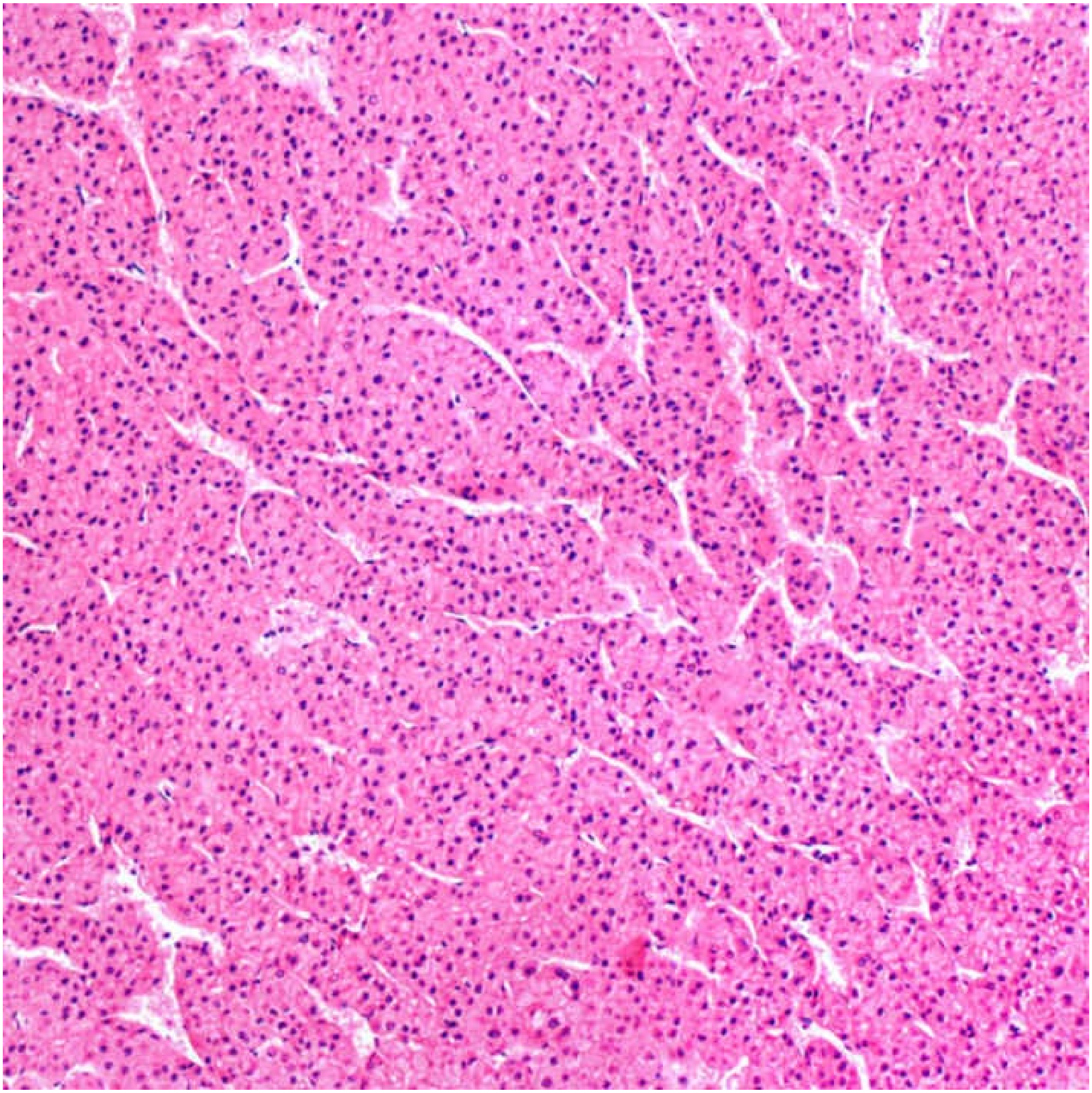


Diffuse Growth Pattern
This example of the diffuse pattern of hepatocellular carcinoma shows innumerable small, white-tan nodules of a tumor in a background of cirrhosis. Careful inspection shows that 2 of these nodules represent gross venous invasion .

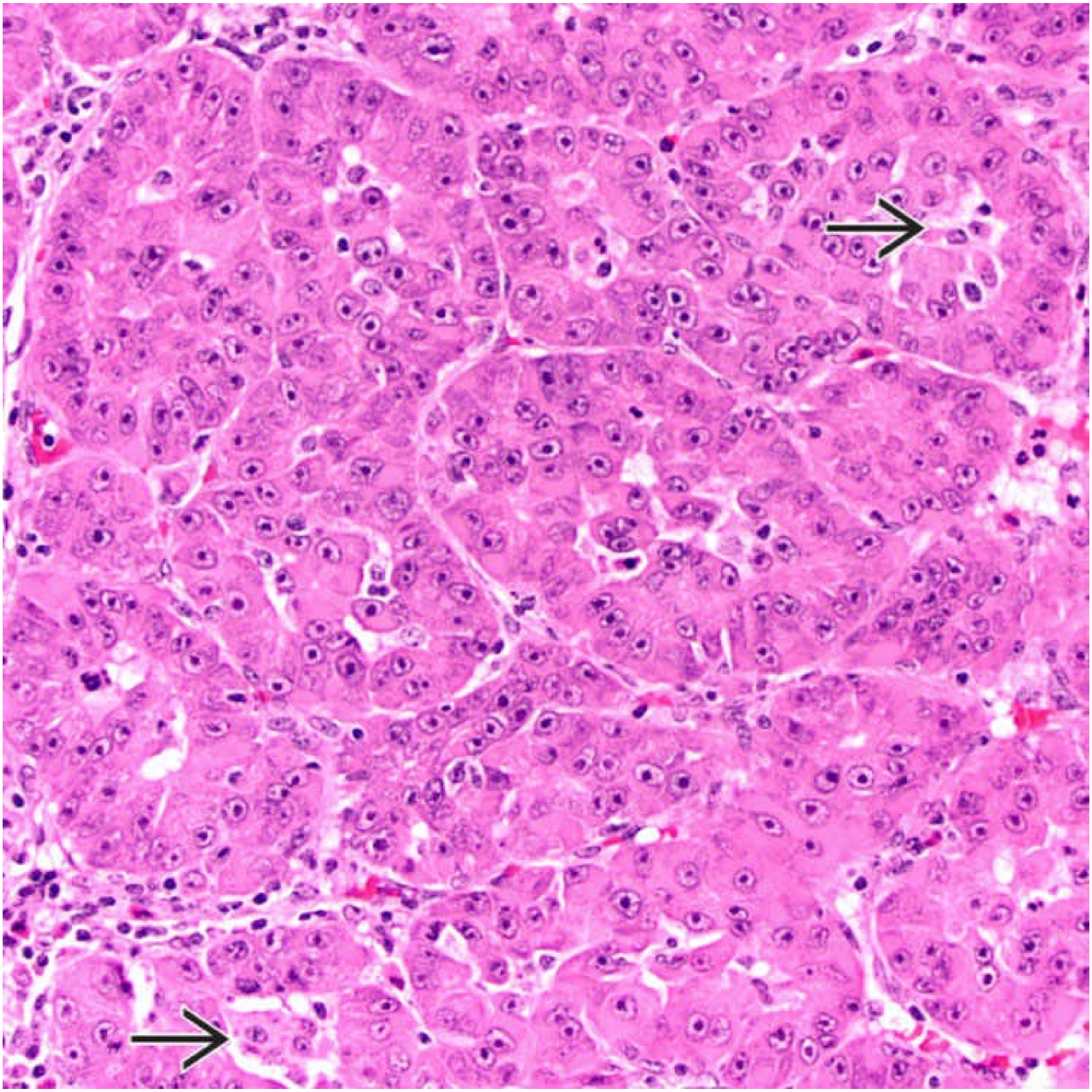


Venous Invasion

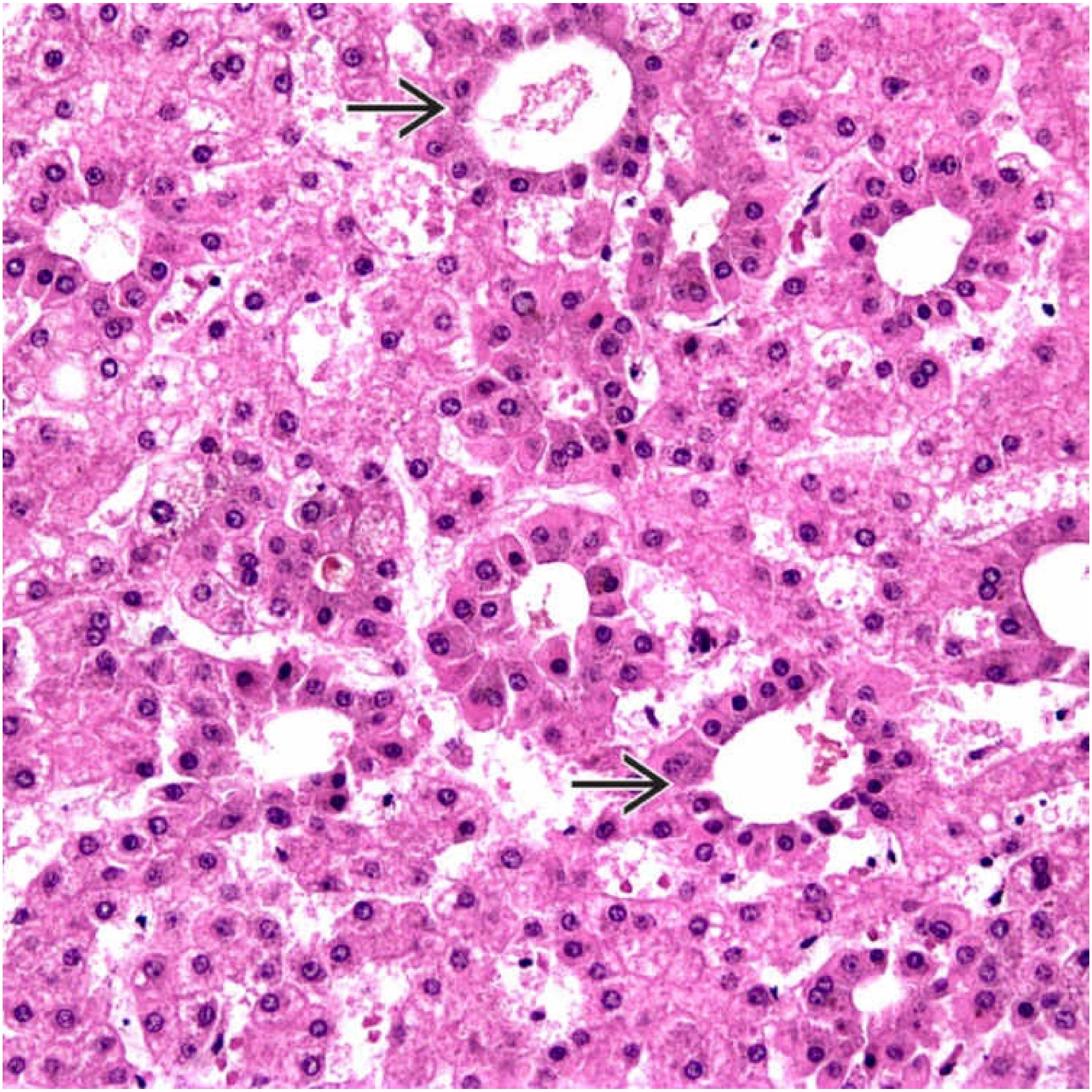
A portal vein is distended and filled with trabeculae of hyperchromatic neoplastic cells. Note the adjacent accompanying bile duct .



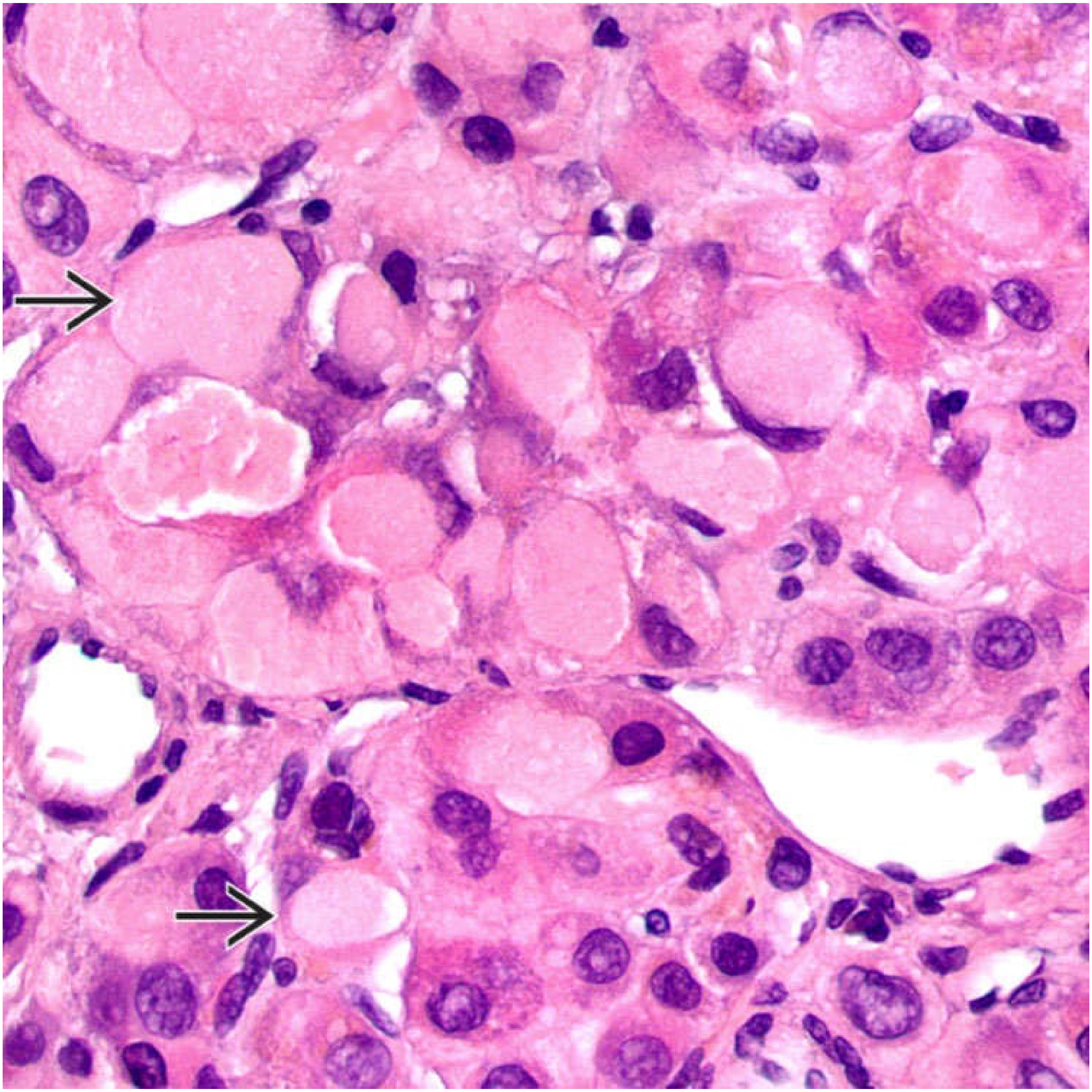
Trabecular Pattern
The tumor cells are arranged in 6- to 8-cell thick trabeculae separated by sinusoids. This is the most common architectural pattern in hepatocellular carcinoma.



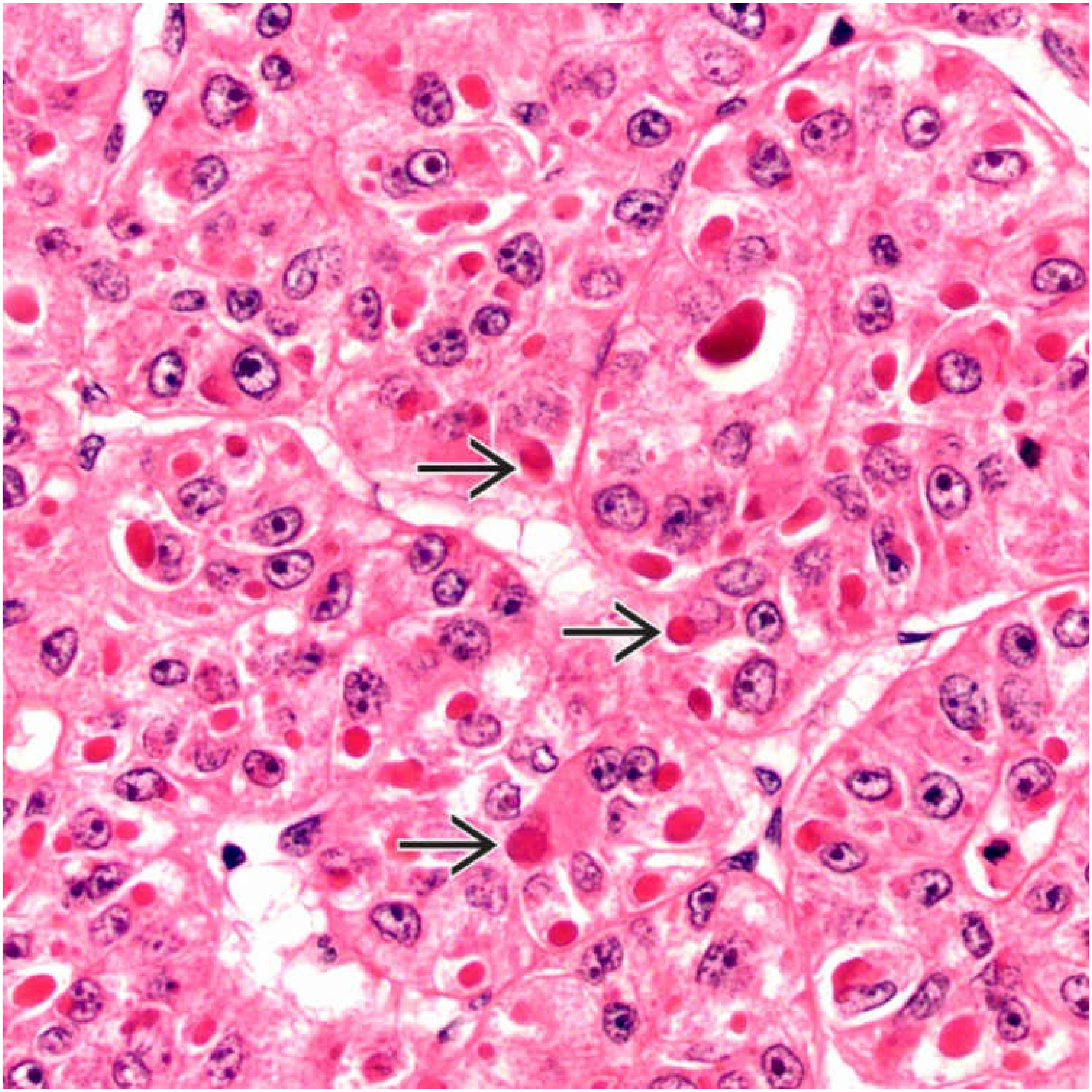
Trabecular Pattern
This image shows hepatocellular carcinoma growing in a pattern of rounded trabeculae with central degenerative changes →.



Pseudoacinar Pattern
A predominantly pseudoacinar pattern in hepatocellular carcinoma can mimic true glands →.

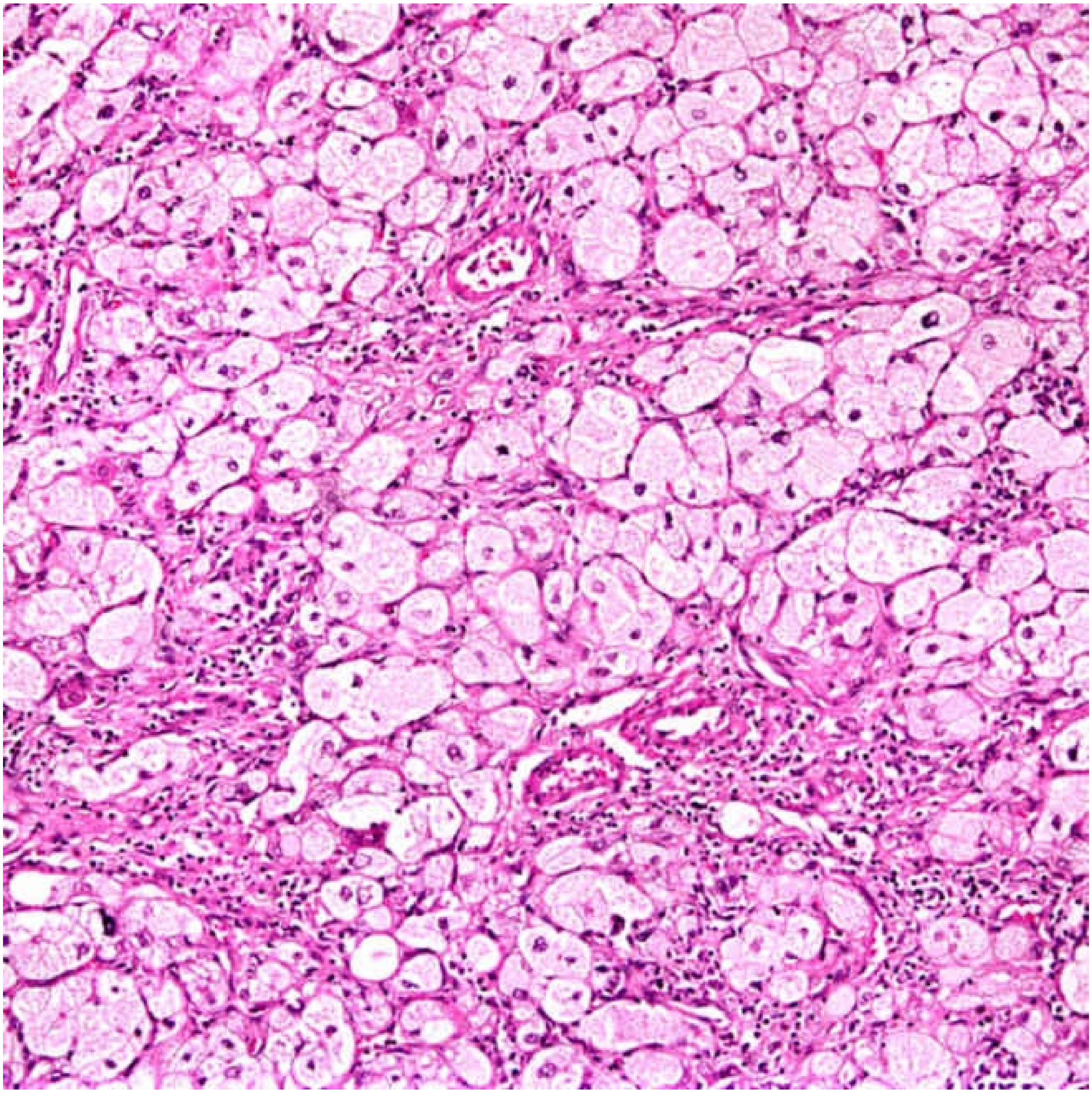


Pale Bodies
This image shows pale eosinophilic cytoplasmic inclusions, presumably fibrinogen, known as pale bodies →. These are more common in fibrolamellar carcinoma.

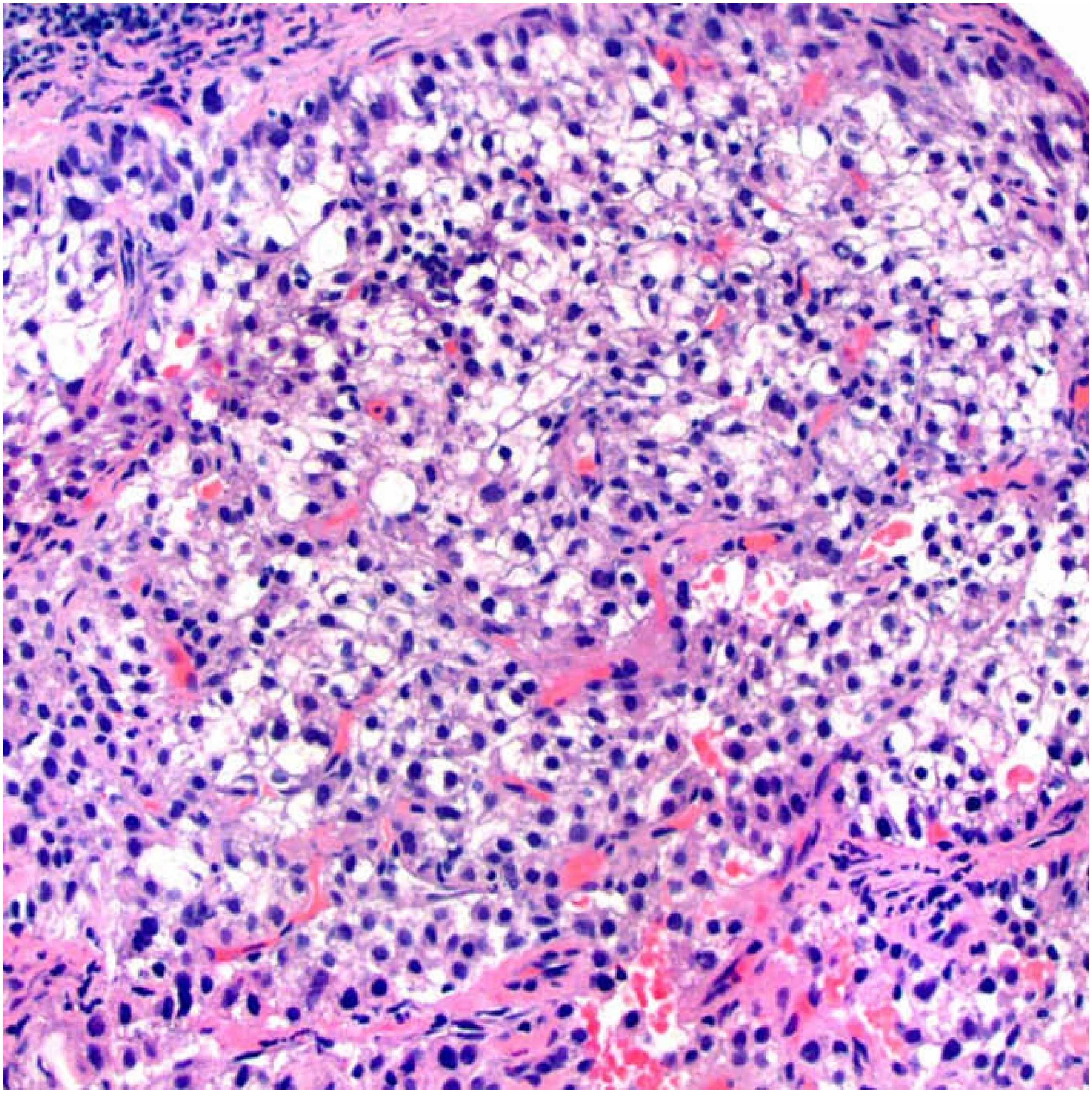


Mallory Hyaline

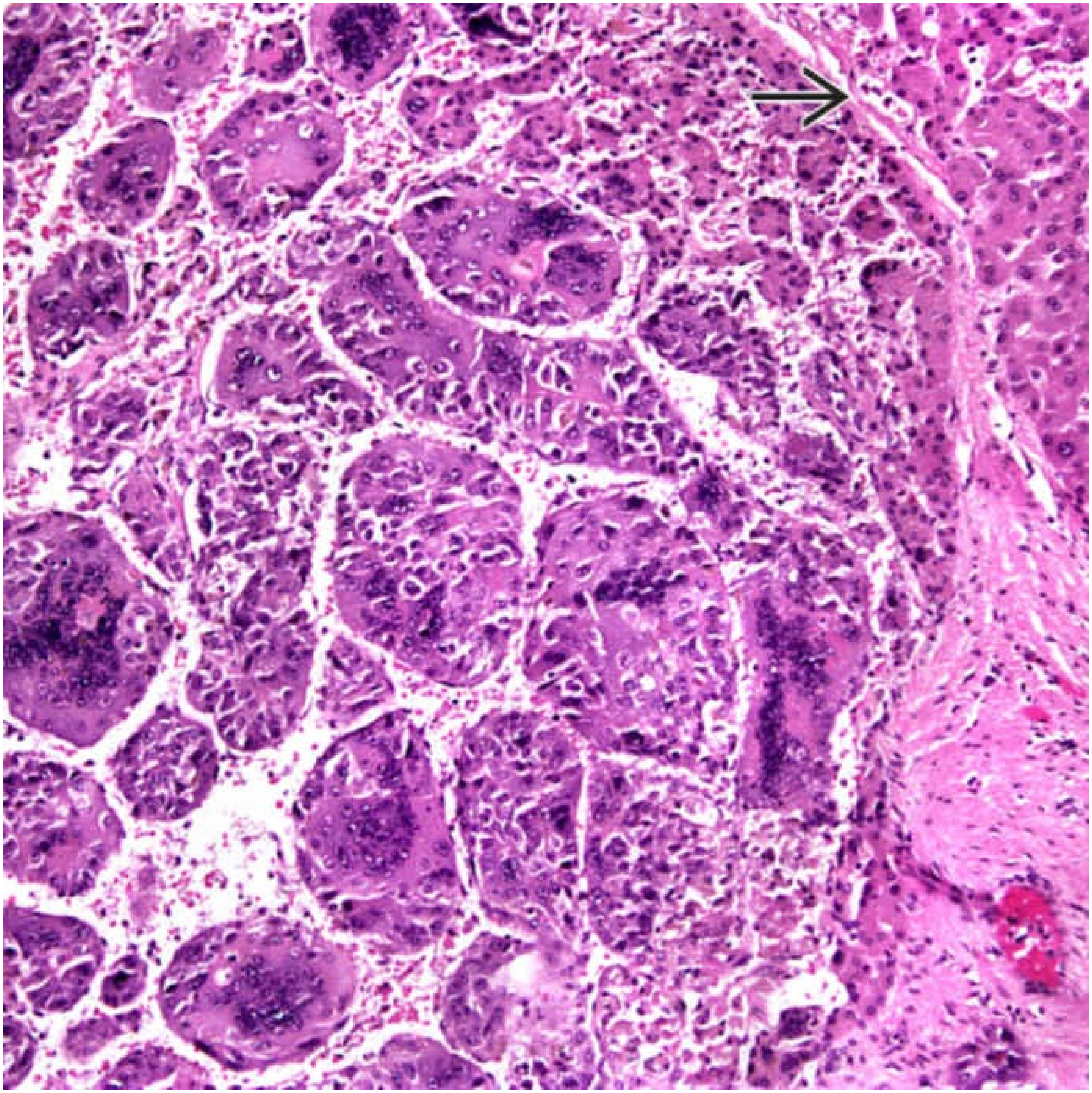
Tumor cells contain an oval eosinophilic inclusion →. Mallory hyaline in hepatocellular carcinoma can have the characteristic ropy appearance of alcoholic hyaline but is often more globular and rounded.



Clear Cell Variant
The tumor cells contain abundant glycogen in the cytoplasm, creating an appearance reminiscent of clear cell renal cell carcinoma.

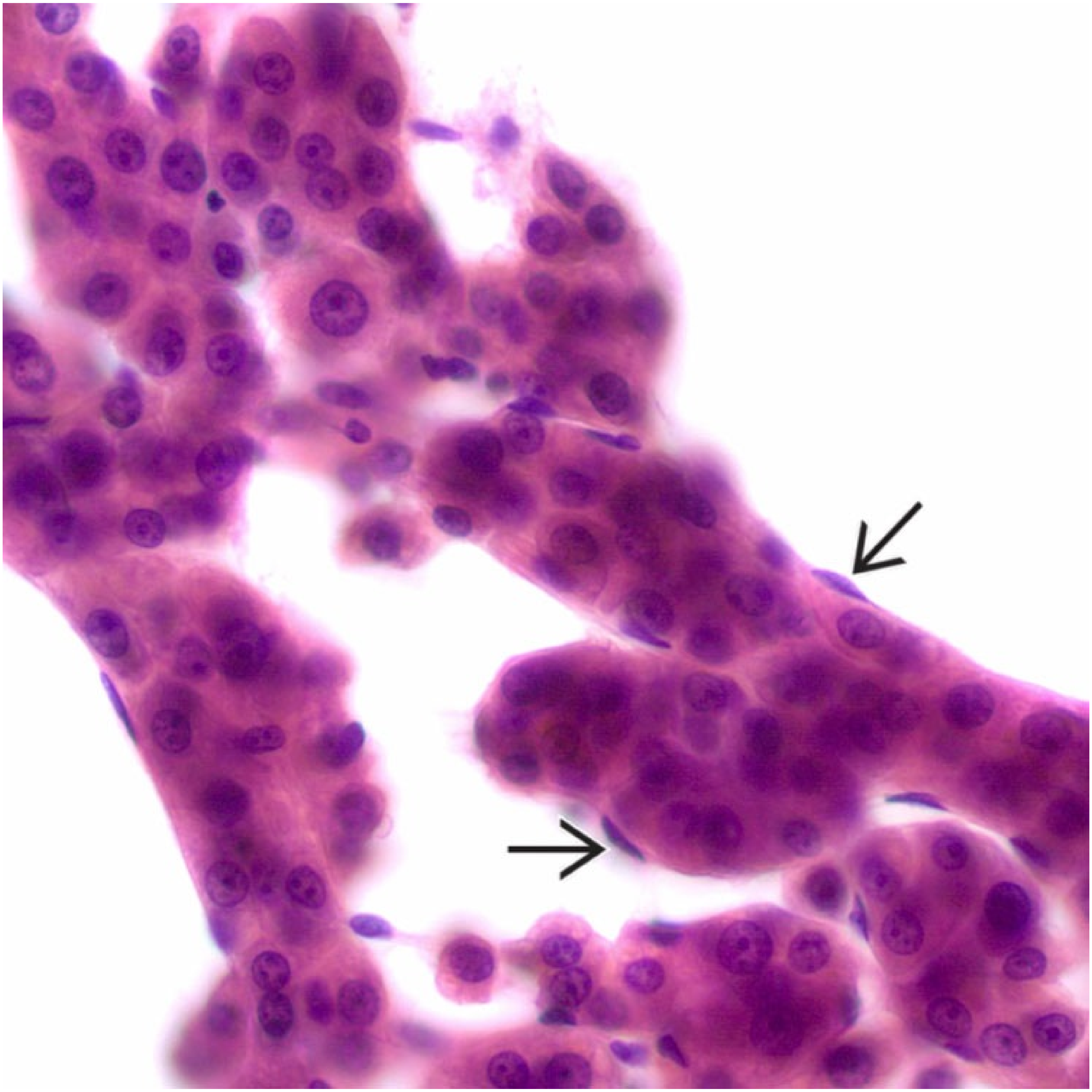


Metastatic Clear Cell Renal Cell Carcinoma
Metastatic renal cell carcinoma is easily mistaken for clear cell variant of hepatocellular carcinoma. This patient had an identical renal tumor excised a few years prior to this tumor developing in the liver.

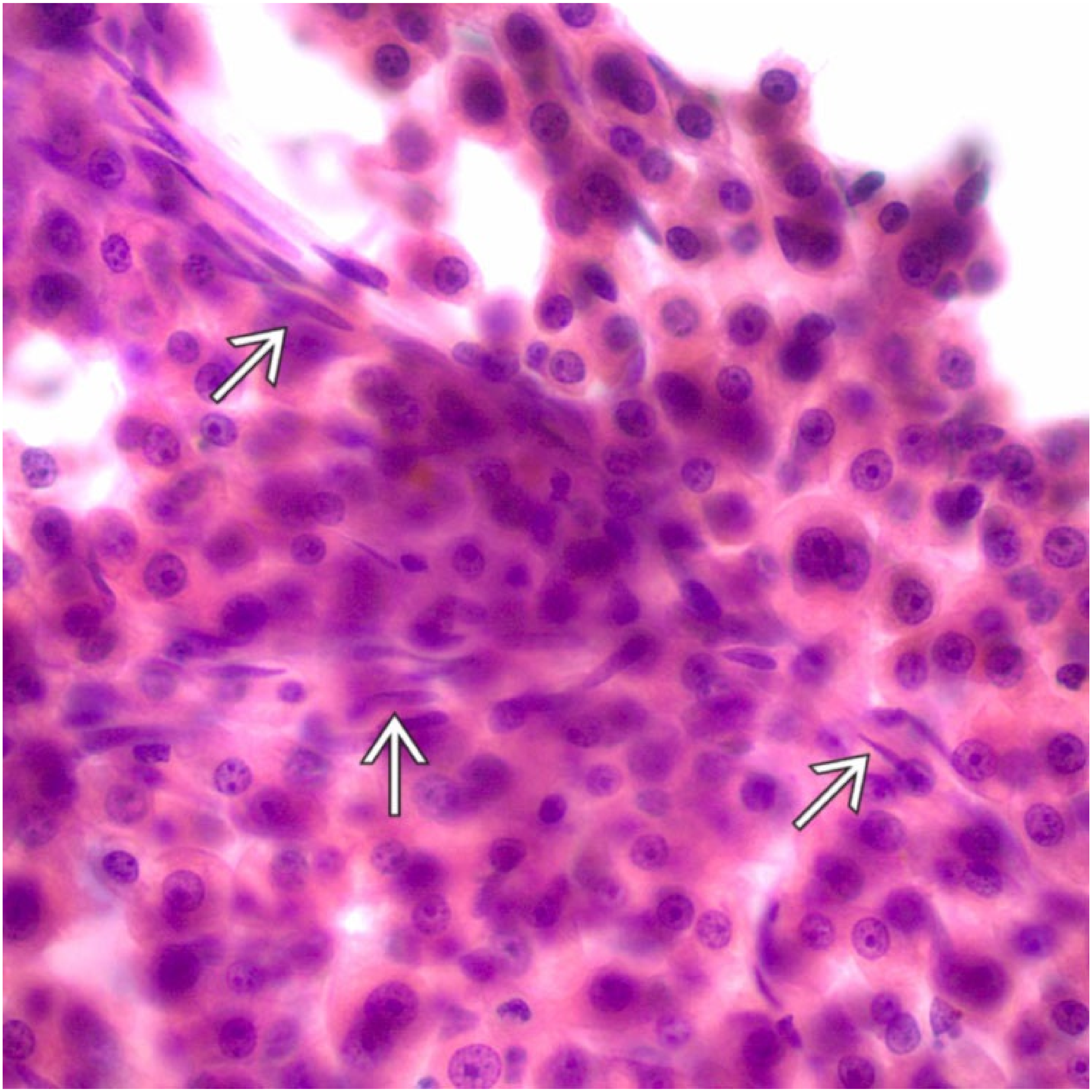


Tumor Giant Cells

This image shows striking multinucleated tumor giant cells in hepatocellular carcinoma. An area of more typical HCC is present at the periphery of the field →.

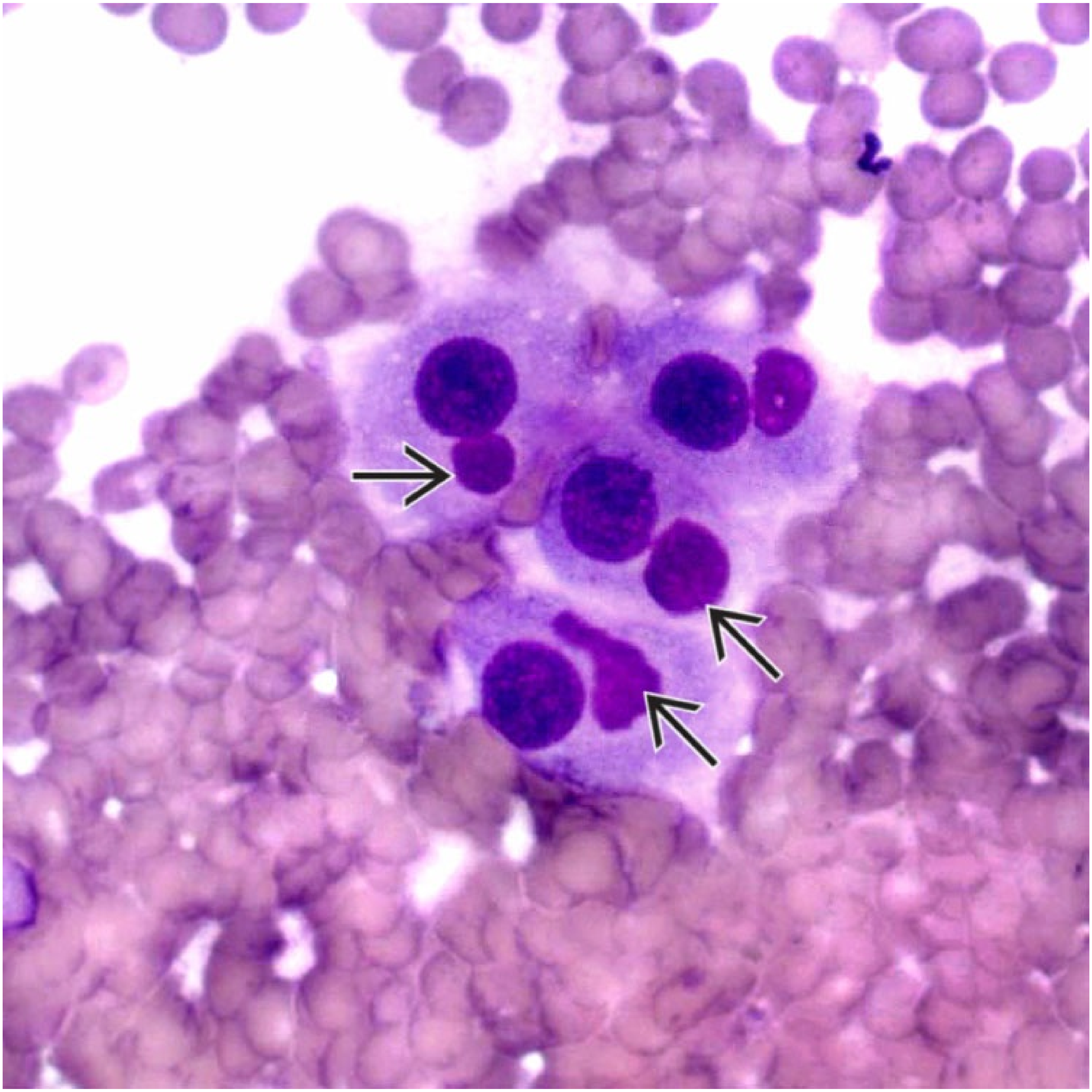


Cytology
Fine-needle aspiration (FNA) biopsy smear of hepatocellular carcinoma shows thick trabeculae of neoplastic hepatocytes. Endothelial wrapping is present at the edges of the tumor →.

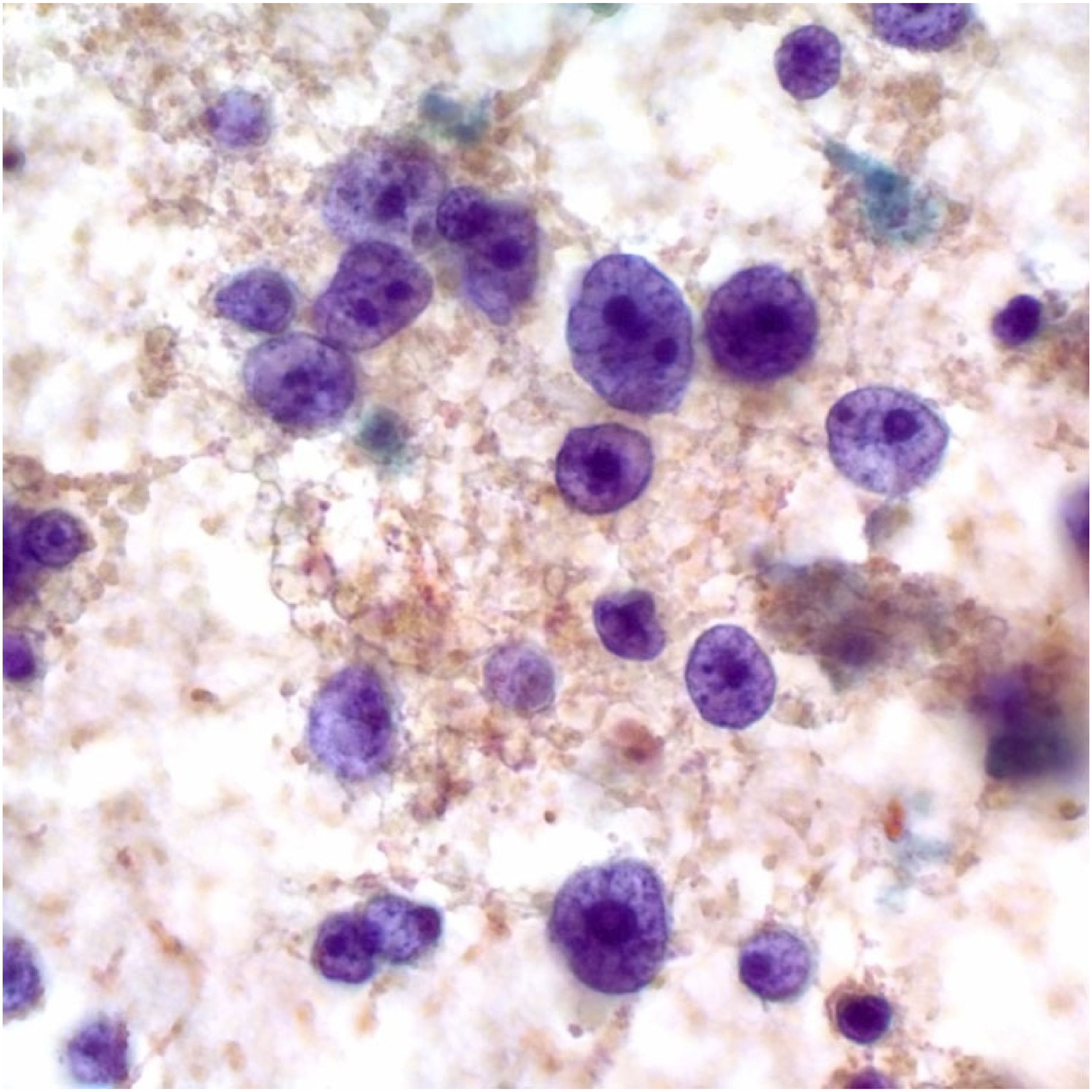


Cytology

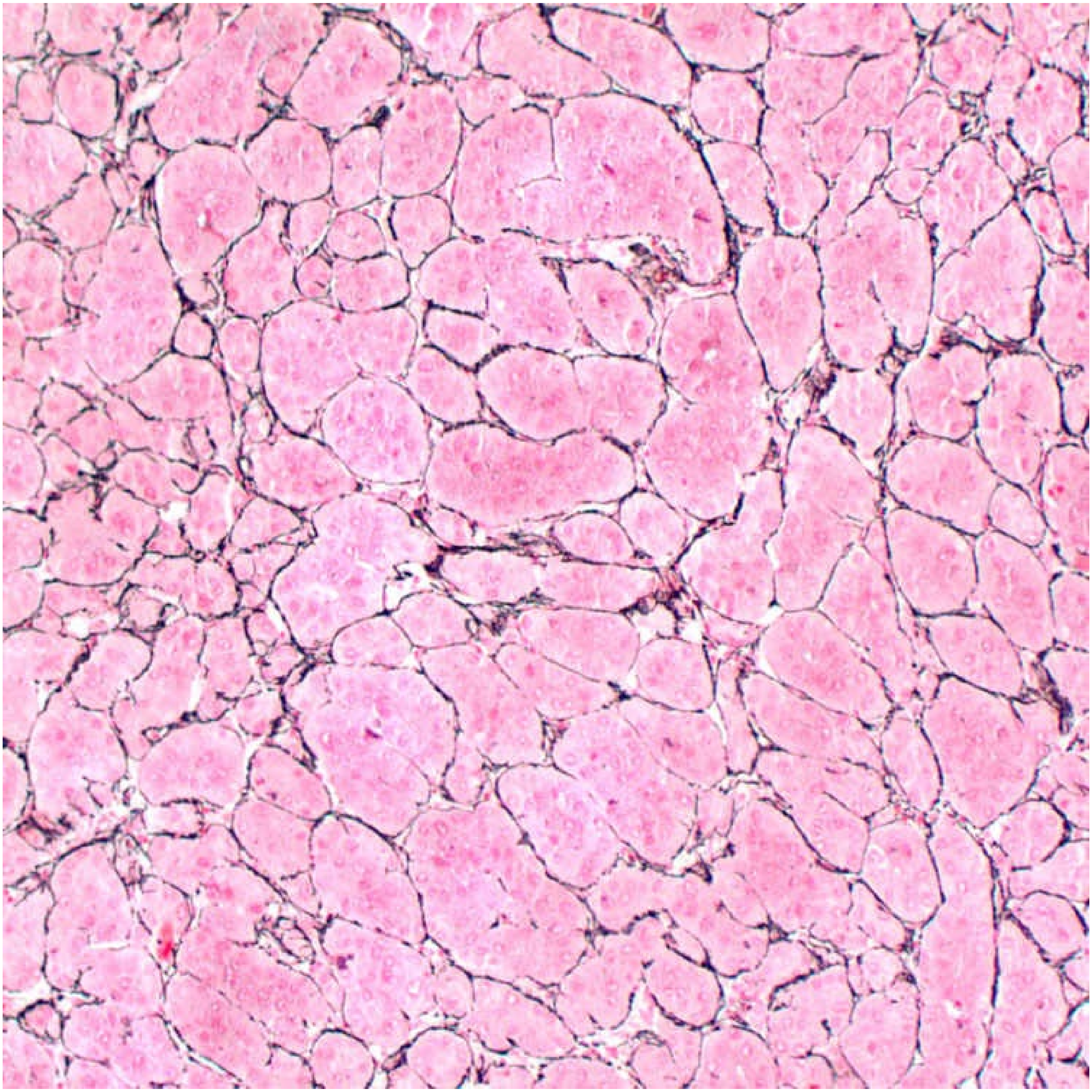
FNA biopsy smear of hepatocellular carcinoma shows a large cluster of neoplastic hepatocytes with traversing blood vessels ⇨ typical of this tumor. A similar phenomenon occurs commonly in renal cell carcinoma.



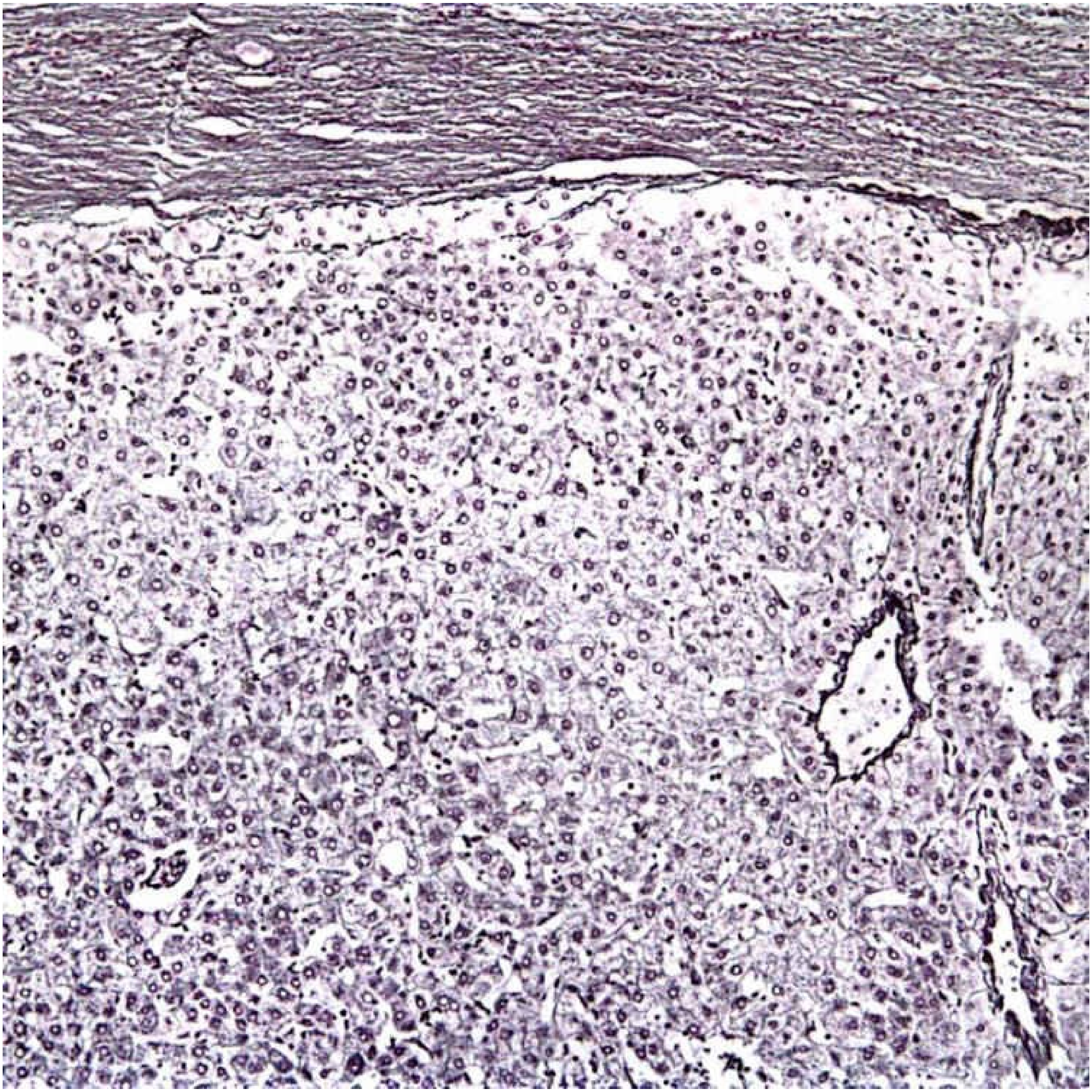
Cytology
In air-dried preparation, the malignant hepatocytes contain cytoplasmic Mallory hyaline →. Note that many of the inclusions are more round or oval than alcohol-related Mallory hyaline.



Cytology
FNA smear shows stripped atypical nuclei, a common pattern in hepatocellular carcinoma. The nuclear enlargement, pleomorphism and prominent nucleoli point toward malignancy.

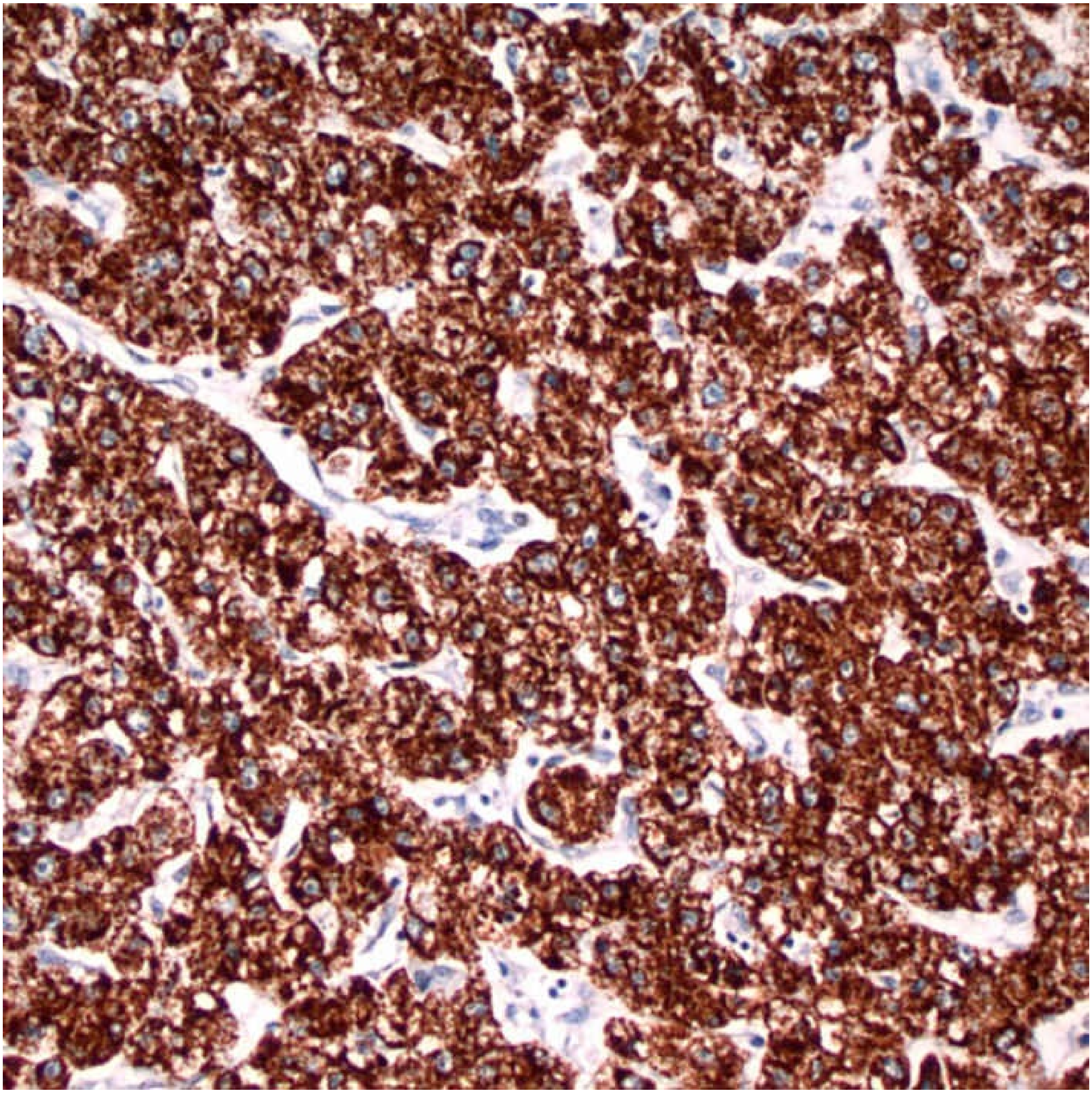


Reticulin Stain
Reticulin stain demonstrates thickened, disorganized trabeculae.

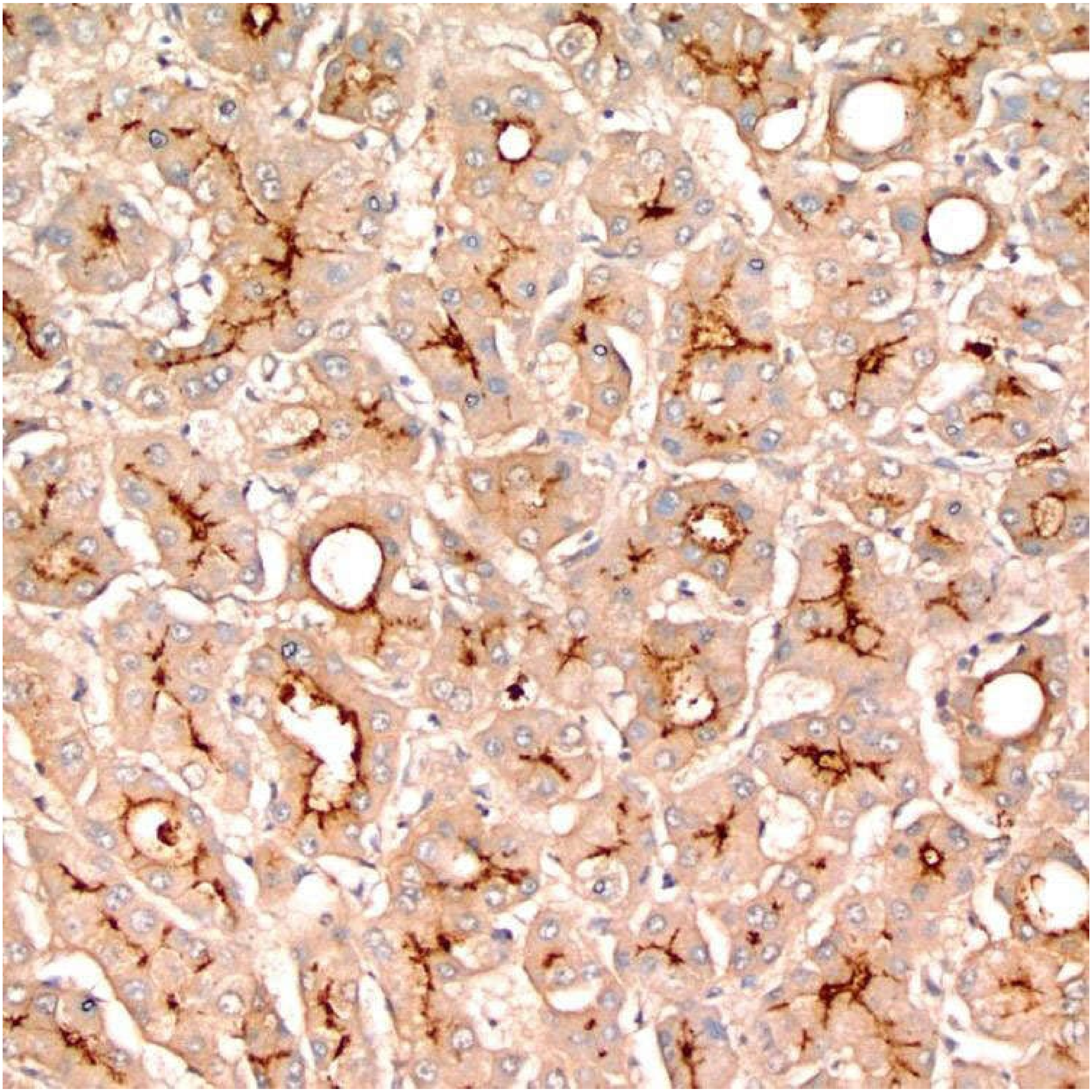


Reticulin Stain

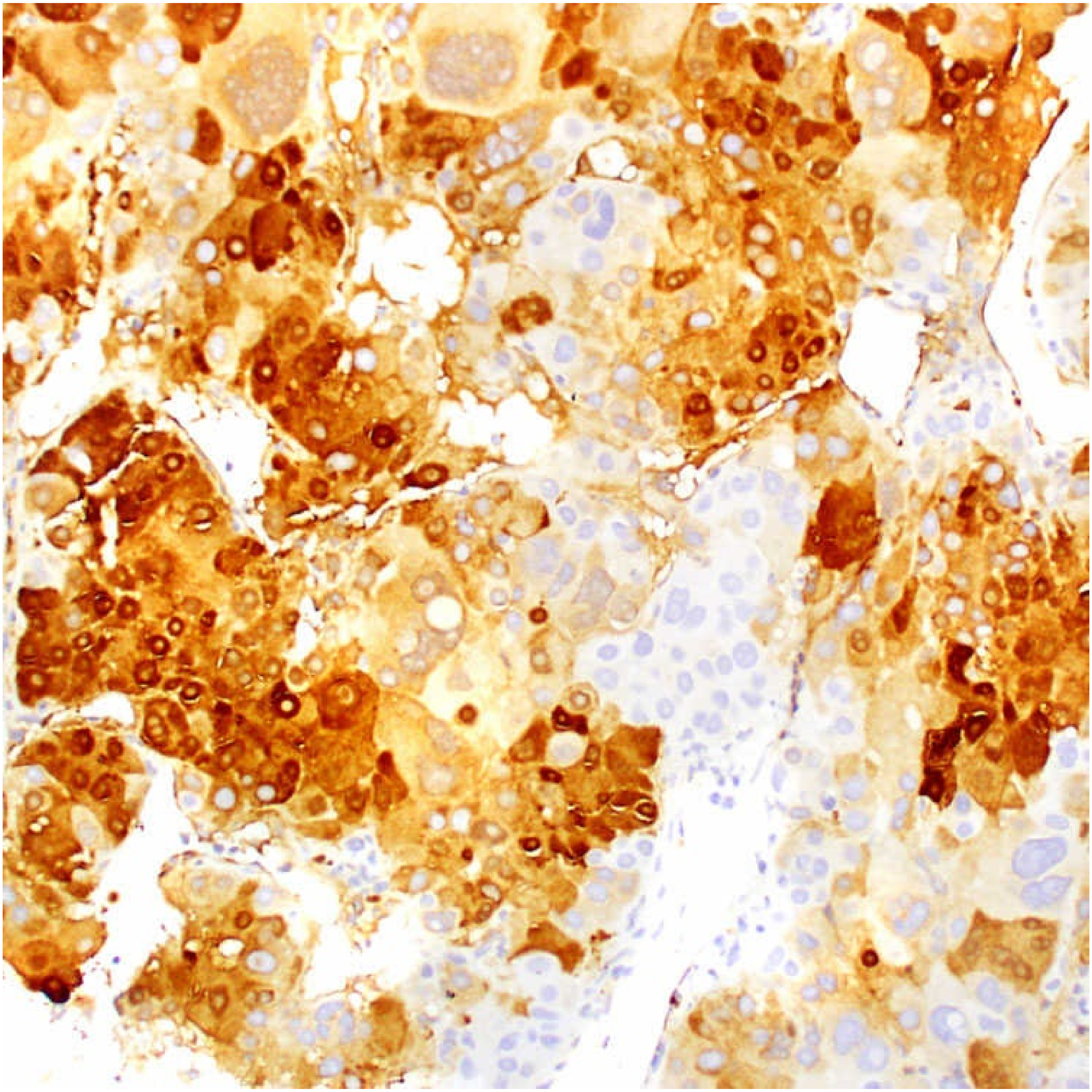
This image shows extensive loss of reticulin network. Loss and fragmentation of the reticulin network is one of the most characteristic and helpful features for the diagnosis, but overt loss may not be seen in very well-differentiated cases.



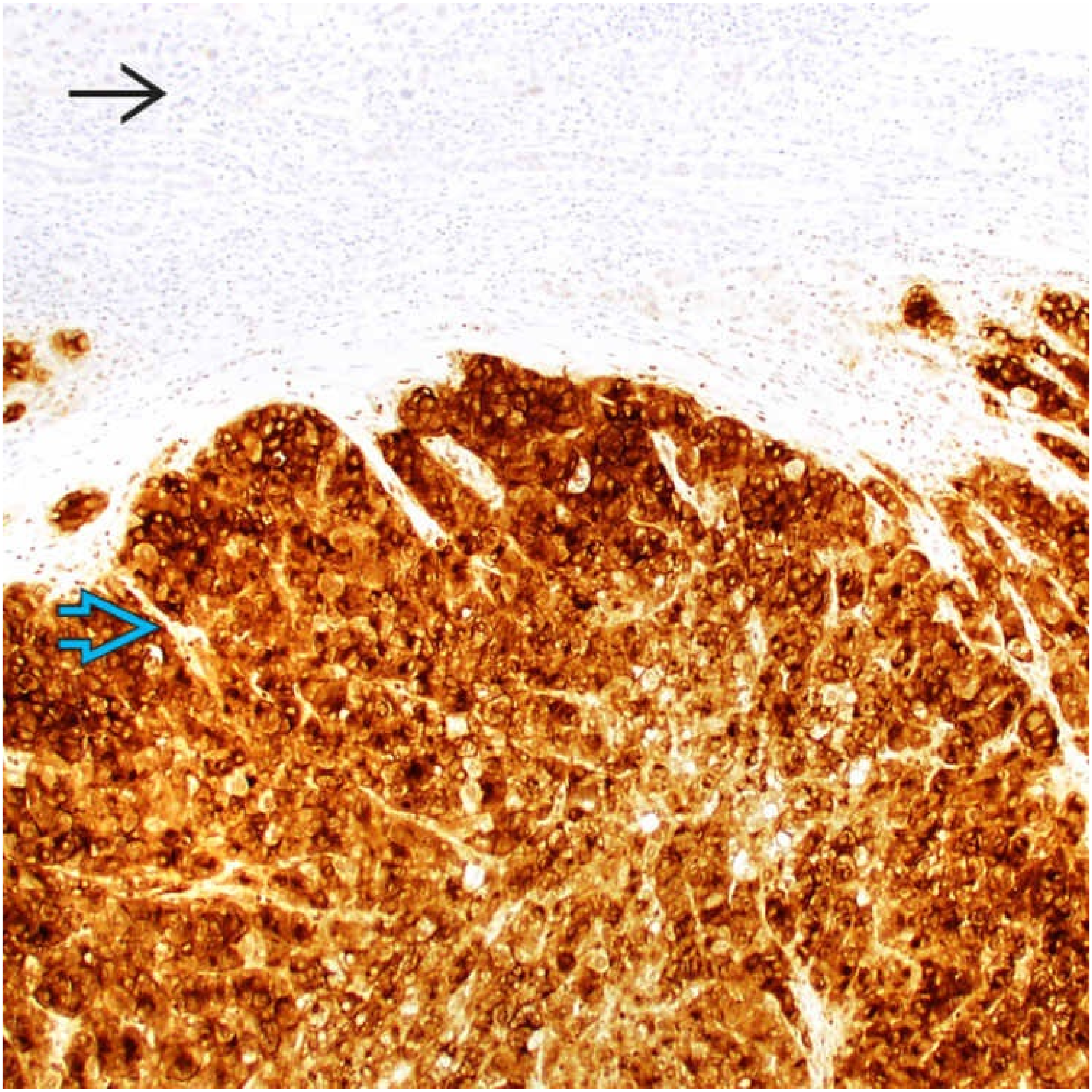
Hep-Par1 Immunostain
This image shows strong, diffuse cytoplasmic positivity with Hep-Par1 immunostaining.



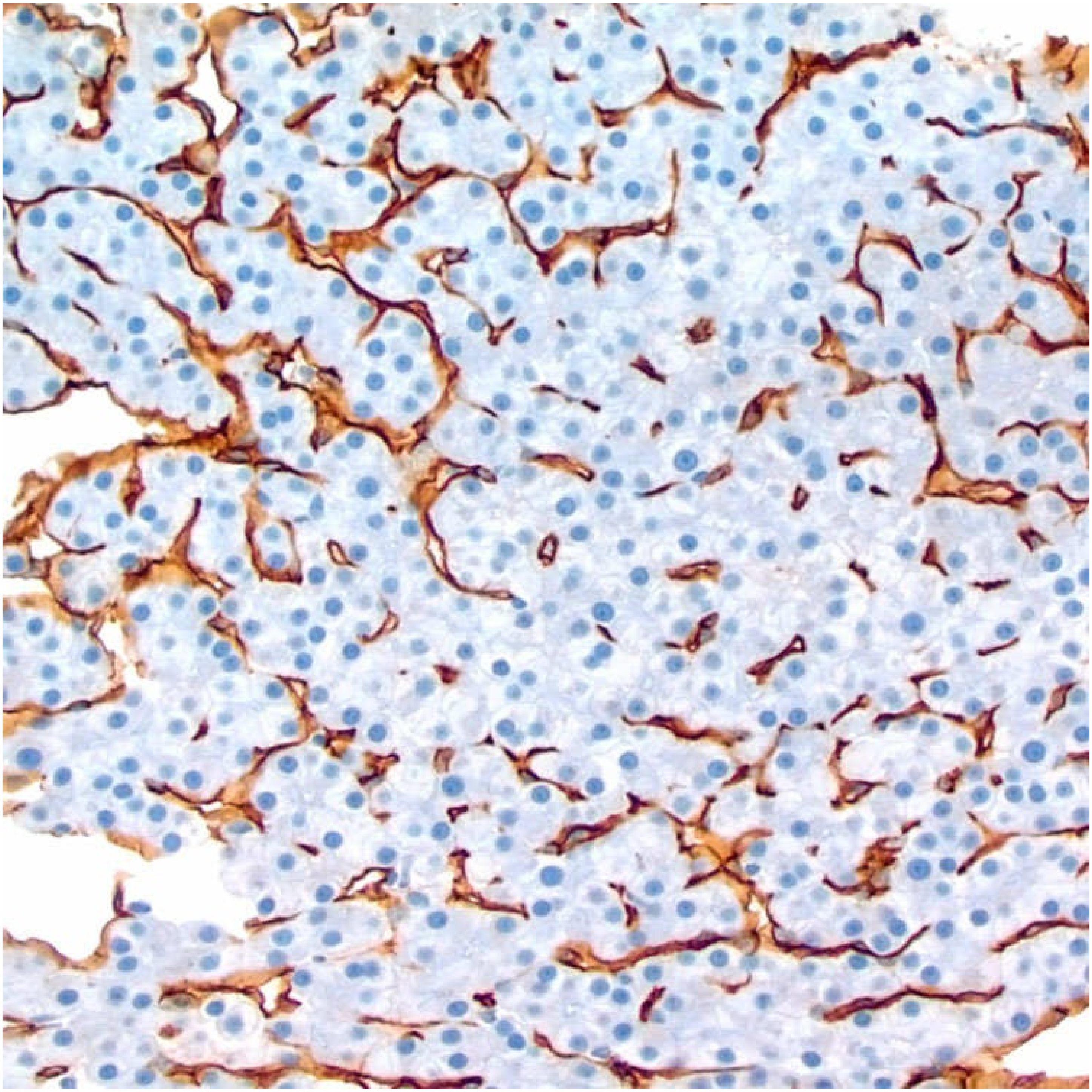
Polyclonal CEA, Canalicular Pattern
Hepatocellular carcinoma shows a characteristic canalicular pattern of staining with polyclonal antibody to carcinoembryonic antigen. This does not work with the monoclonal antibody. Adenocarcinomas typically show luminal or cytoplasmic staining.



Arginase-1 Immunohistochemistry
Poorly differentiated HCC shows cytoplasmic staining with arginase-1. This is one of the most sensitive markers for HCC, and a vast majority of poorly differentiated cases are positive.

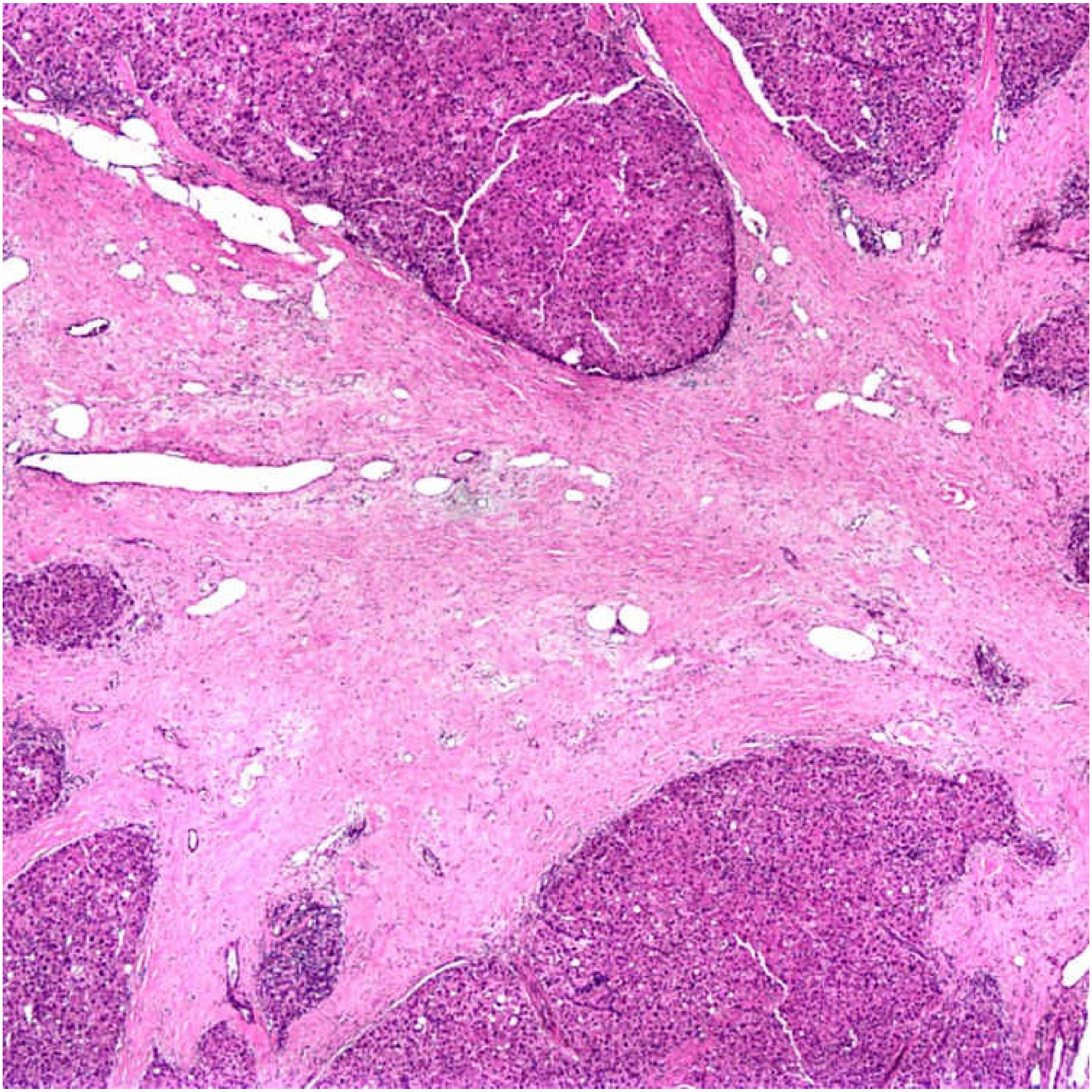


Glypican-3 Immunohistochemistry
Glypican-3 is an oncofetal antigen that shows cytoplasmic staining in the majority of HCC cases, especially those with poor differentiation. Nonneoplastic liver is negative.

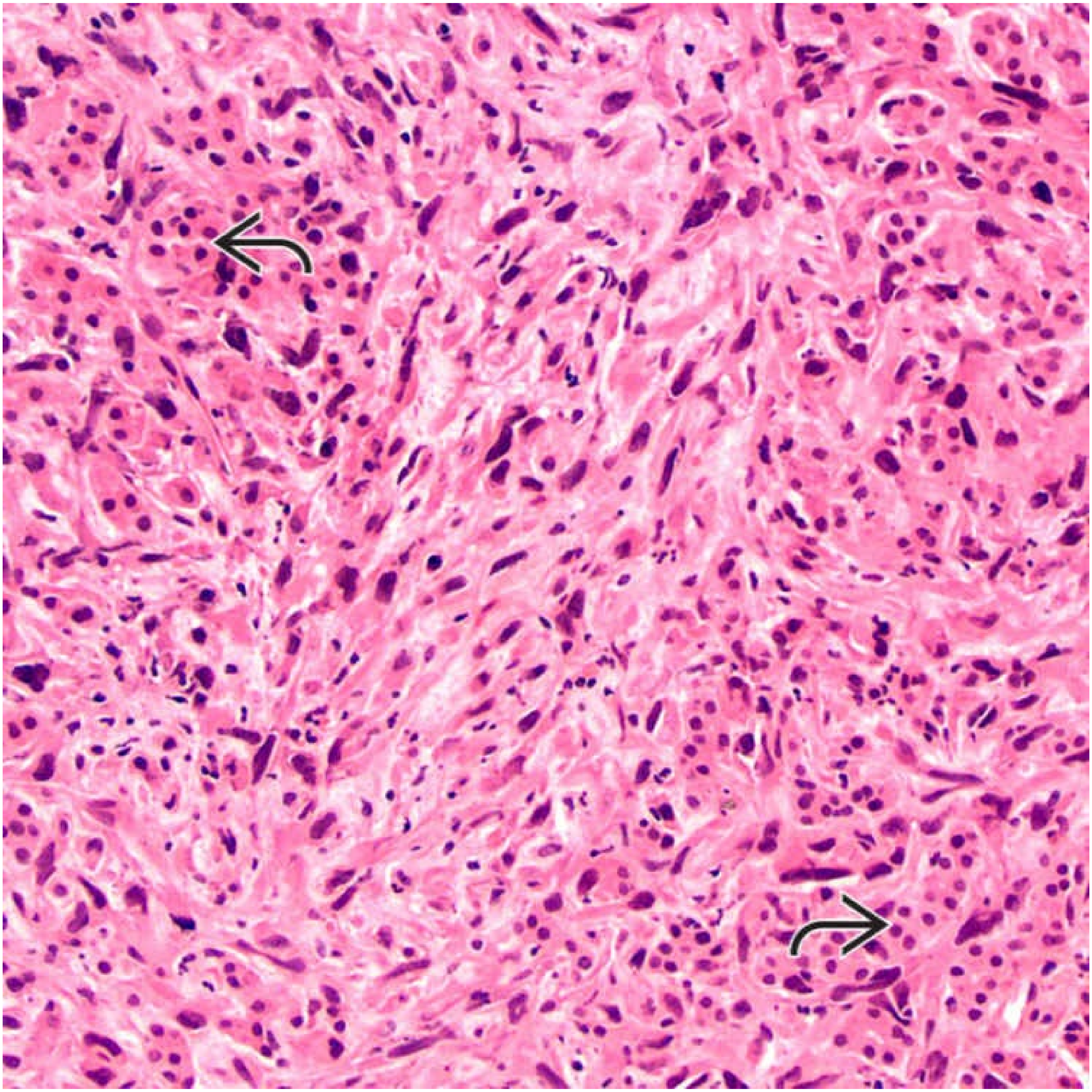


CD34 Immunostain

This image shows diffuse sinusoidal staining. The sinusoids in hepatocellular carcinoma become “capillarized,” and thus express antigens normally found in capillary endothelium but not in normal sinusoidal endothelium.

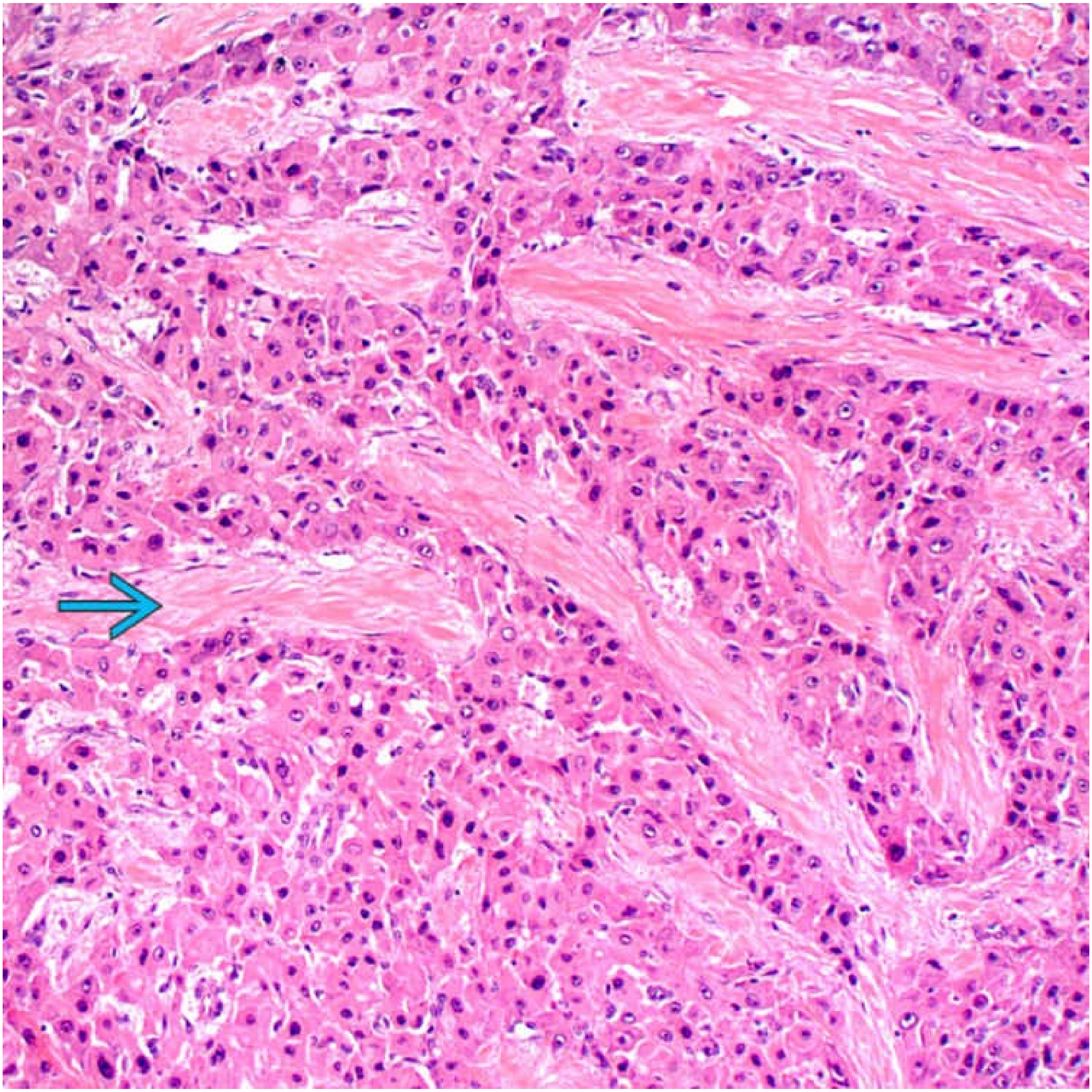


Scirrhous Variant
The tumor has prominent fibrous stroma and may have a large central fibrous scar that can mimic focal nodular hyperplasia or fibrolamellar hepatocellular carcinoma.

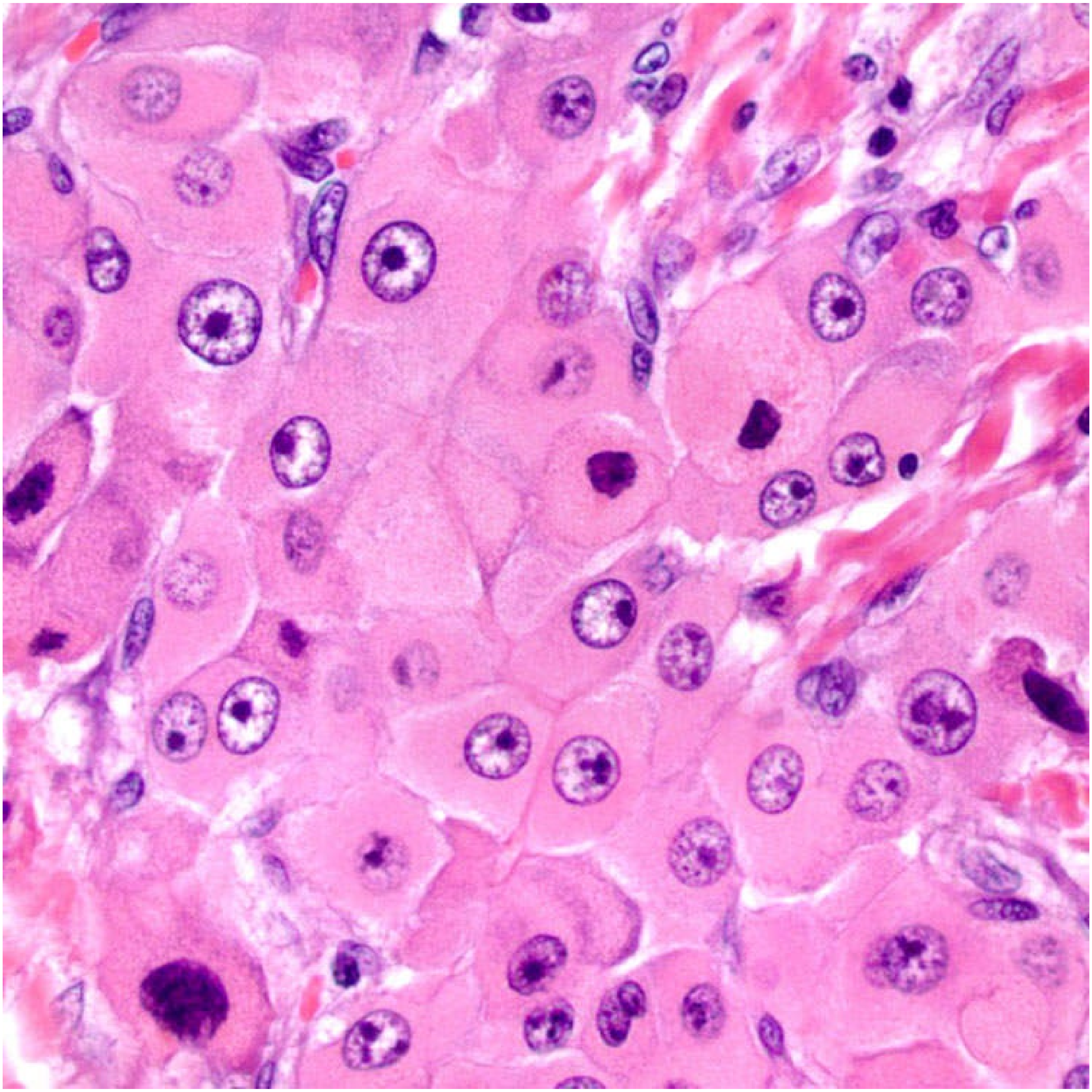


Sarcomatoid Variant
This image shows interlacing fascicles of spindle-shaped tumor cells with more compact epithelioid tumor cells .

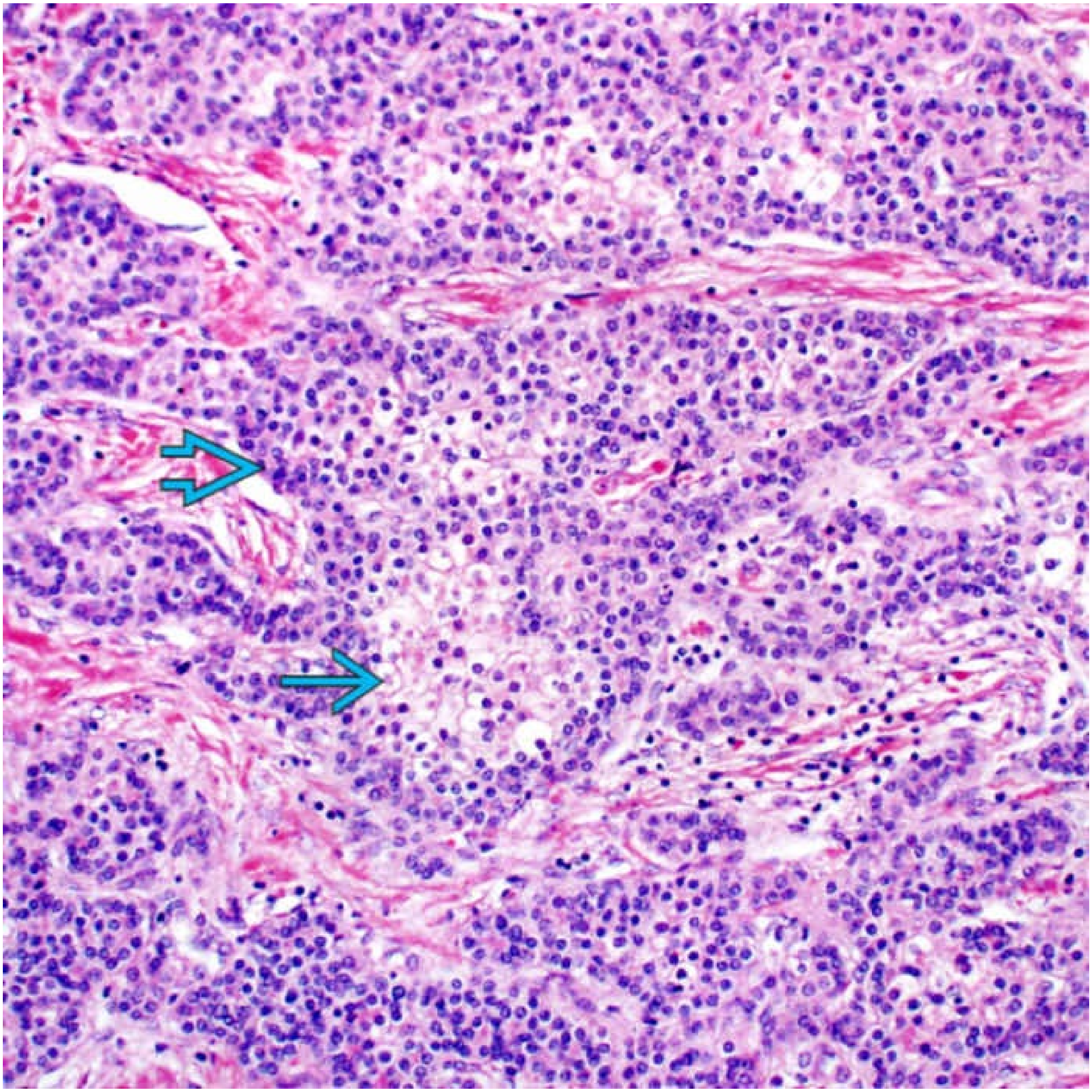
Fibrolamellar Carcinoma
Clinically, this tumor in a young woman was thought to be focal nodular hyperplasia. Note the lobular growth pattern and central scar ⇨, which can be seen in both focal nodular hyperplasia and fibrolamellar carcinoma.



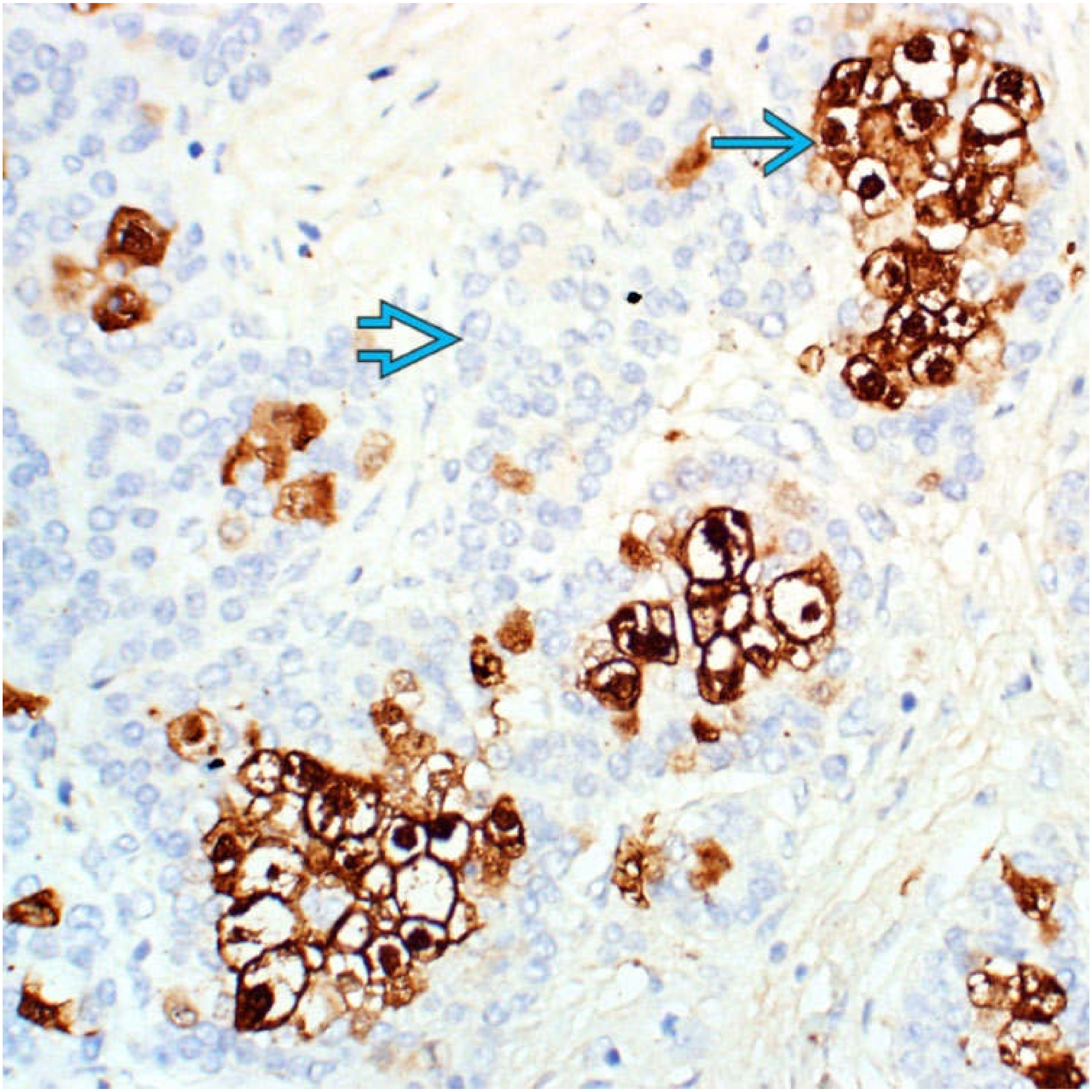
Fibrolamellar Carcinoma
This image shows fibrous septa composed of parallel collagen fibers → separating tumor trabeculae.



Fibrolamellar Carcinoma
The tumor cells are large, eosinophilic, and polygonal. They have large, vesicular nuclei with prominent nucleoli. The eosinophilic granular cytoplasm is due to large numbers of mitochondria.



HCC With Stem Cell Features
H&E shows polygonal hepatoid cells toward the center of tumor cell nests and small uniform cells toward the periphery of the nests. These small tumor cells often have uniform nuclei and scant cytoplasm, and they are proposed to be tumor stem cells.



Arginase Immunohistochemistry
HCC with putative stem cell features shows that the hepatoid cells are arginase (+) →, while the smaller stem cells are (-) ⇨. Various markers like CD56, CD133, KIT, CK19, etc., have been proposed as stem cell markers, but none of these is specific for progenitor cells.

SELECTED REFERENCES

1. Graham, RP, et al. DNAJB1-PRKACA is specific for fibrolamellar carcinoma. *Mod Pathol*. 2015; 28(6):822–829.
2. Chen, J, et al. The stratifying value of Hangzhou criteria in liver transplantation for hepatocellular carcinoma. *PLoS One*. 2014; 9(3):e93128.
3. Honeyman, JN, et al. Detection of a recurrent DNAJB1-PRKACA chimeric transcript in fibrolamellar hepatocellular carcinoma. *Science*. 2014; 343(6174):1010–1014.

4. Mitchell, DG, et al. LI-RADS (Liver Imaging Reporting and Data System): Summary, discussion, consensus of the LI-RADS Management Working Group and future directions. *Hepatology*. 2014. [ePub].
5. Osada, M, et al. Combination of hepatocellular markers is useful for prognostication in gastric hepatoid adenocarcinoma. *Hum Pathol*. 2014; 45(6):1243–1250.
6. Krings, G, et al. Immunohistochemical pitfalls and the importance of glypican 3 and arginase in the diagnosis of scirrhous hepatocellular carcinoma. *Mod Pathol*. 2013; 26(6):782–791.
7. Bruix, J, et al. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011; 53(3):1020–1022.
8. Ross, HM, et al. Fibrolamellar carcinomas are positive for CD68. *Mod Pathol*. 2011; 24(3):390–395.
9. Jakate, S, et al. Diffuse cirrhosis-like hepatocellular carcinoma: a clinically and radiographically undetected variant mimicking cirrhosis. *Am J Surg Pathol*. 2010; 34(7):935–941.
10. Salomao, M, et al. Steatohepatitic hepatocellular carcinoma (SH-HCC): a distinctive histological variant of HCC in hepatitis C virus-related cirrhosis with associated NAFLD/NASH. *Am J Surg Pathol*. 2010; 34(11):1630–1636.
11. Yan, BC, et al. Arginase-1: a new immunohistochemical marker of hepatocytes and hepatocellular neoplasms. *Am J Surg Pathol*. 2010; 34(8):1147–1154.
12. Fanni, D, et al. Cytokeratin 20-positive hepatocellular carcinoma. *Eur J Histochem*. 2009; 53(4):269–273.
13. Kakar, S, et al. Clinicopathologic features and survival in fibrolamellar carcinoma: comparison with conventional hepatocellular carcinoma with and without cirrhosis. *Mod Pathol*. 2005; 18(11):1417–1423.
14. Stuart, KE, et al. Hepatocellular carcinoma in the United States. Prognostic features, treatment outcome, and survival. *Cancer*. 1996; 77(11):2217–2222.
15. Hurlimann, J, et al. Immunohistochemistry in the differential diagnosis of liver carcinomas. *Am J Surg Pathol*. 1991; 15(3):280–288.
16. Kassianides, C, et al. The clinical manifestations and natural history of hepatocellular carcinoma. *Gastroenterol Clin North Am*. 1987; 16(4):553–562.
17. Kew, MC, et al. Hepatocellular carcinoma in urban born blacks: frequency and relation to hepatitis B virus infection. *Br Med J (Clin Res Ed)*. 1986; 293(6558):1339–1341.
18. Craig, JR, et al. Fibrolamellar carcinoma of the liver: a tumor of adolescents and young adults with distinctive clinico-pathologic features. *Cancer*. 1980; 46(2):372–379.

Hepatoblastoma

KEY FACTS

Etiology/Pathogenesis

• Aberrant *Wnt* /β-catenin activation

Clinical Issues

• Most common malignant liver neoplasm in children
• Most patients have increased serum α-fetoprotein
• Key prognostic factor of survival is tumor stage

Microscopic

• Most common component is epithelial subtypes
  ○ Pure fetal epithelial histology is associated with favorable prognosis
  ○ Embryonal and fetal epithelial patterns often seen together
  ○ Macrotrabecular is composed of fetal or embryonal type cells in wide trabeculae
  ○ Small undifferentiated component is associated with poorer prognosis
• Mixed hepatoblastoma (HB) are composed of epithelial and mesenchymal components
  ○ Mesenchymal component can range from immature spindle cells to fibrous tissue
  ○ Osteoid-like and teratoid elements can occur

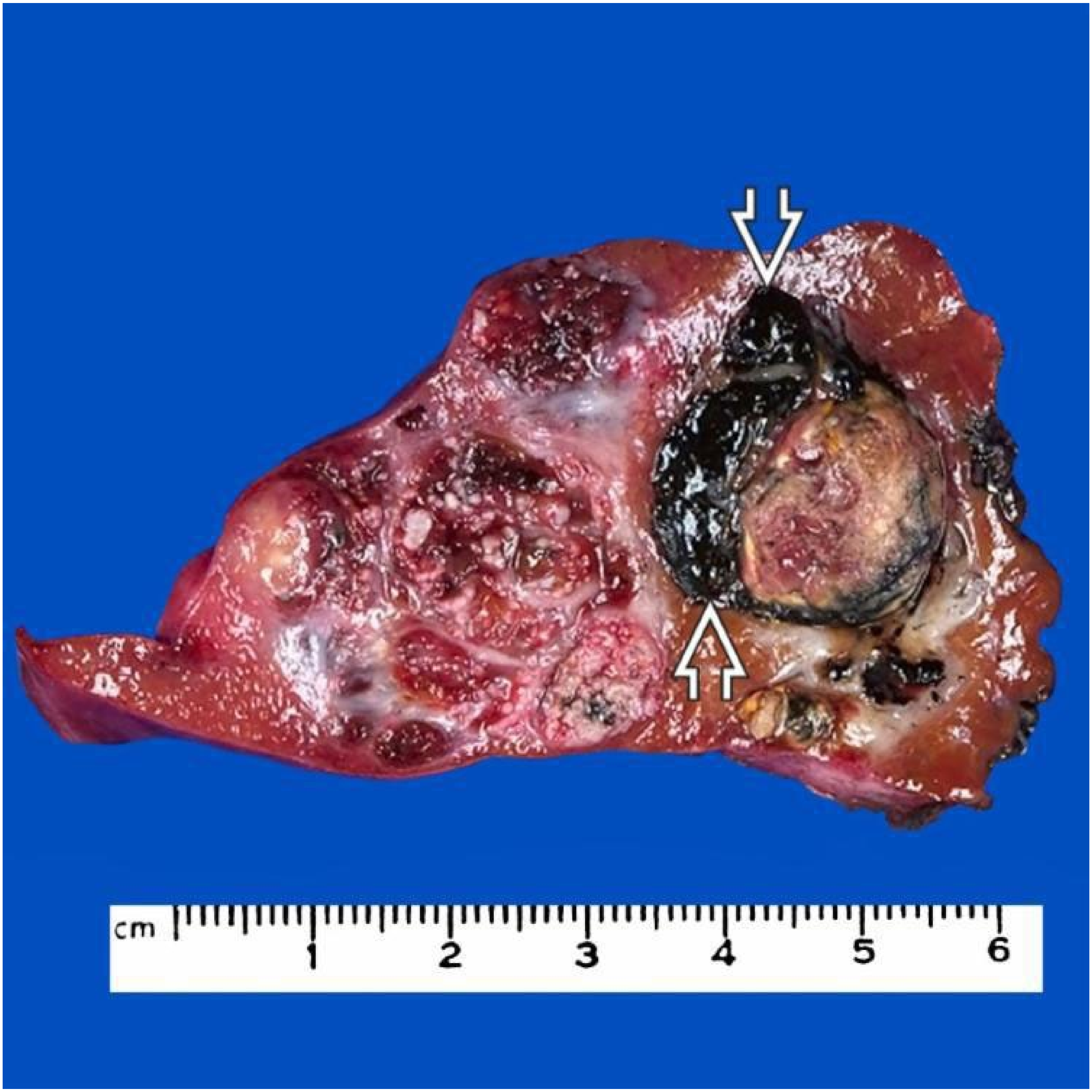
Ancillary Tests

• Nuclear β-catenin staining in epithelial and mesenchymal components (70% of cases), often membranous in fetal pattern
• Positive glypican-3 and Hep-Par1 staining in fetal and embryonal epithelial cells
• Positive glutamine synthetase staining in fetal and variably in embryonal cells

Top Differential Diagnoses

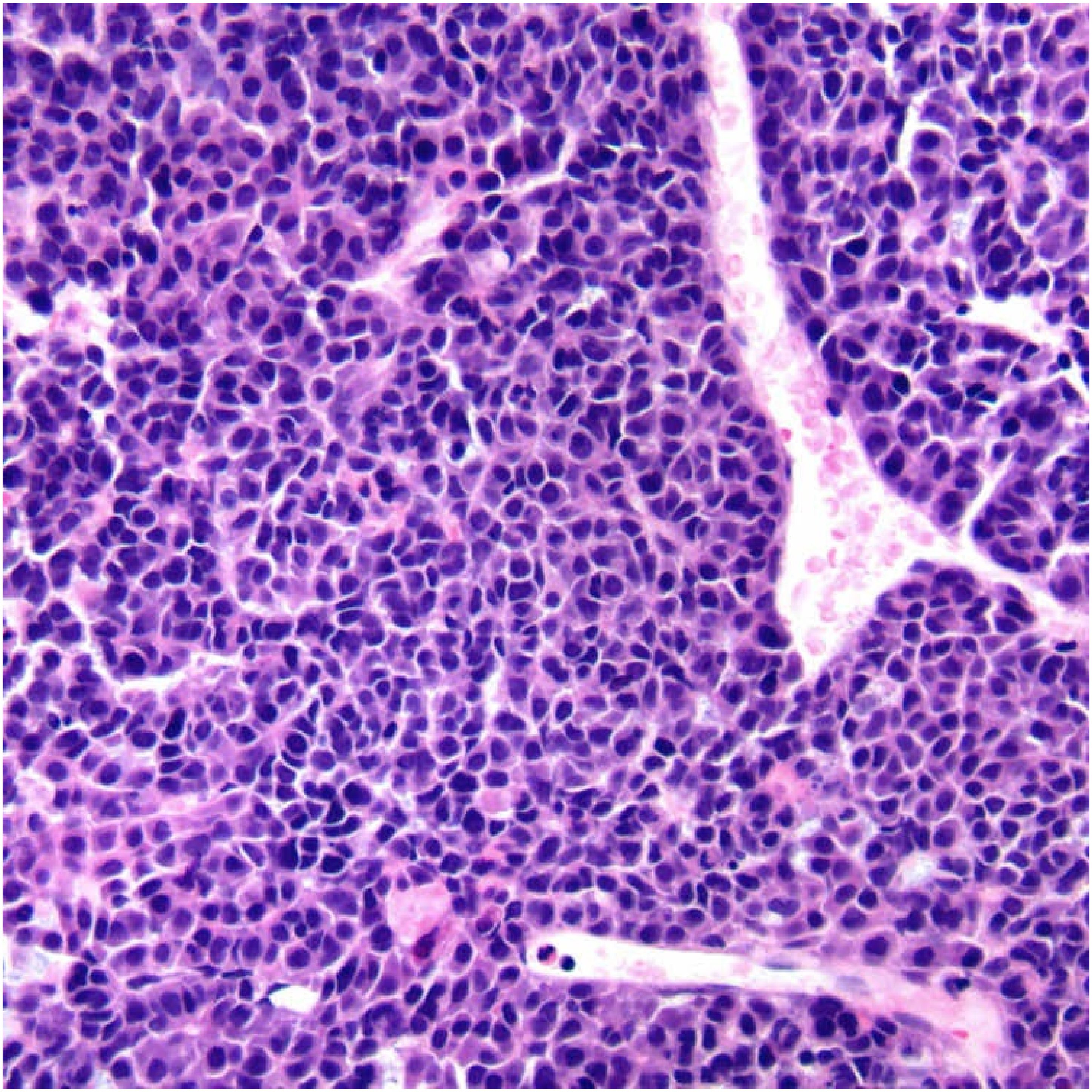
• Normal liver parenchyma; positive nuclear &/or cytoplasmic β-catenin staining in HB

• Hepatocellular carcinoma; presence of both fetal and embryonal patterns diagnostic of HB



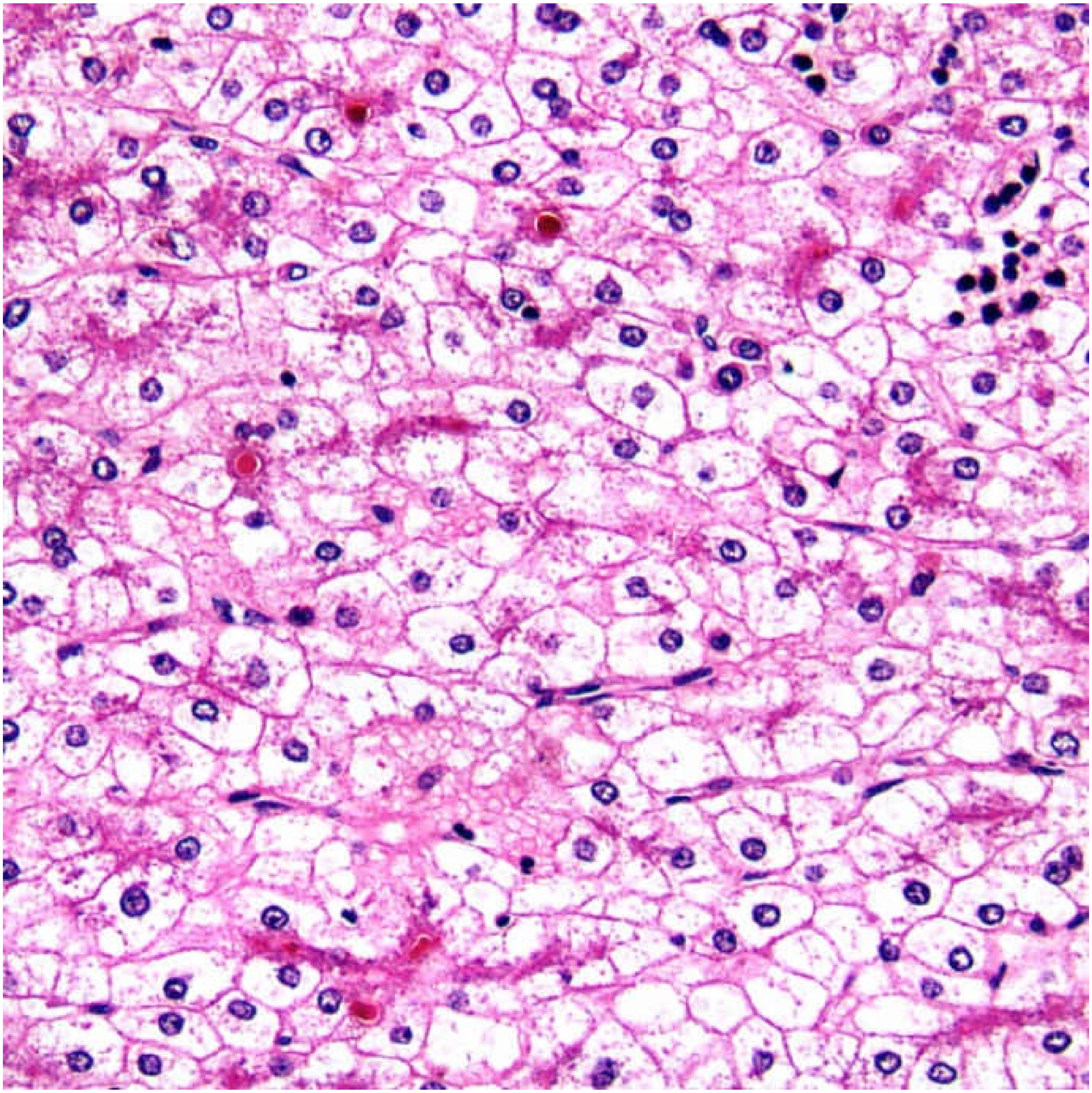
Treated Hepatoblastoma, Gross

This tumor was treated with preoperative chemotherapy and was diagnosed as a mixed epithelial and mesenchymal hepatoblastoma with teratoid features. The black focus ⇨ contained melanin pigment.

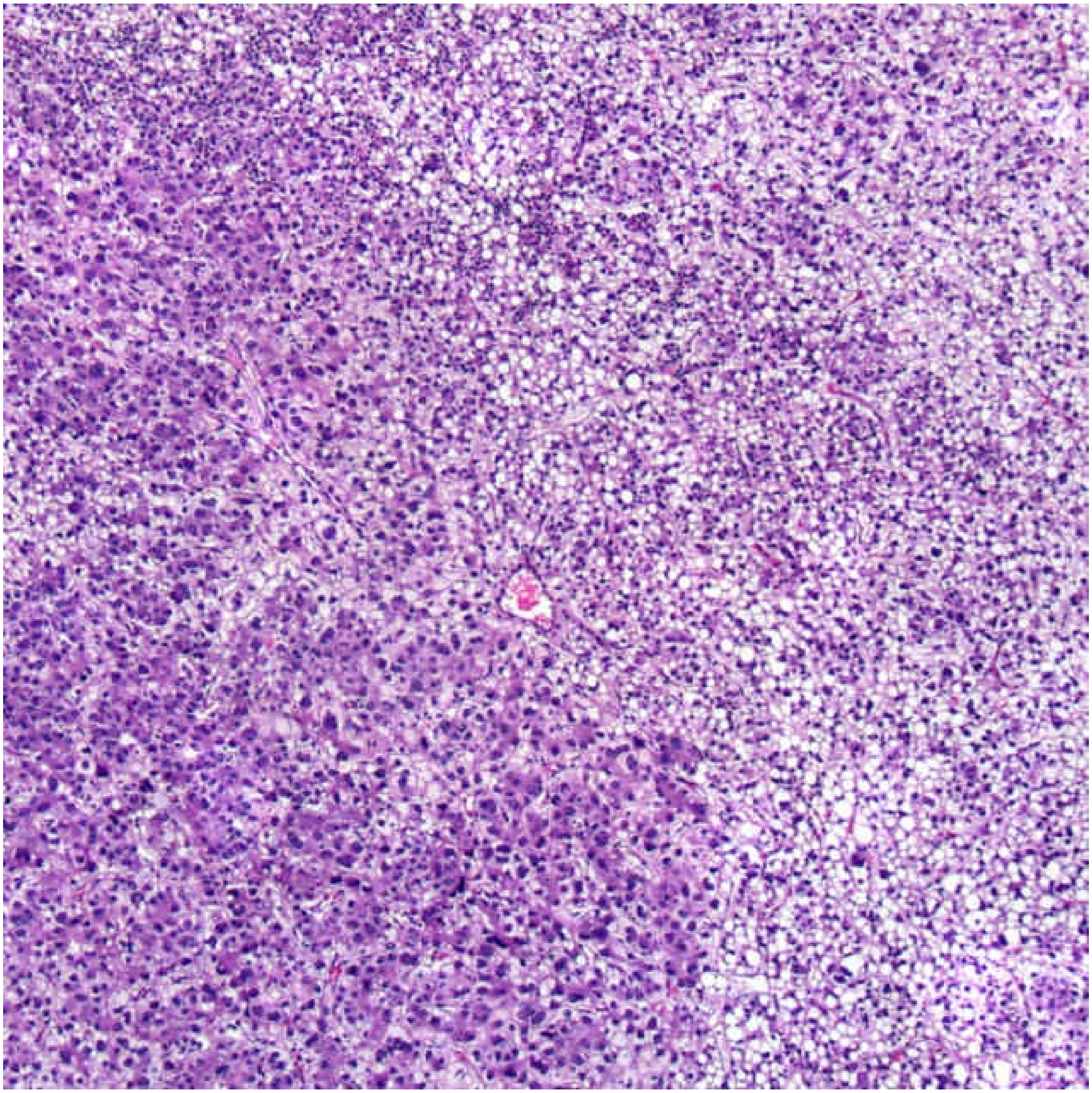


Embryonal Pattern

H&E shows sheets and poorly formed nests of embryonal epithelial cells with angulated nuclei and less cytoplasm than fetal epithelial cells, which can often coexist in the same tumor. Embryonal cells have nuclear or cytoplasmic reactivity to β-catenin and are diffusely positive for glypican-3.



Pure Fetal Histology
H&E shows uniform polygonal cells that are smaller than normal hepatocytes with round nuclei, no nucleoli, clear cytoplasm, and no mitotic activity.


Pure Fetal Histology
Light and dark appearance is due to variable amounts of glycogen or cytoplasmic lipid. If the entire tumor has this appearance and mitotic activity ≤ 2/10 HPF, it would be classified as pure fetal histology.

TERMINOLOGY

Abbreviations

- Hepatoblastoma (HB)

Definitions

- Predominantly pediatric liver tumor that mimics developing fetal or embryonal liver histologically

ETIOLOGY/PATHOGENESIS

Neoplasm

- *Wnt* pathway activation in 70-90% due to β-catenin mutation

CLINICAL ISSUES

Epidemiology

- Incidence
  - 2.1% of all pediatric cancers (1-19 years)
  - Higher in low birth weight infants
- Age
  - Most common malignant liver neoplasm in children
    - 88% in children ≤ 5 years and 3% > 15 years
    - Mean age at diagnosis is 19 months
- Sex
  - Male predominance (M:F = 3:2)

Site

- 58% involve right lobe, 27% involve both lobes

Presentation

- Painless abdominal mass, hepatomegaly

Laboratory Tests

- Increased serum α-fetoprotein in 75-96% of patients
  - Often ≥ 100,000 ng/mL
  - Caveat: High AFP normal before 6 months of age
  - Useful marker of response to therapy and recurrence

Treatment

- Surgical resection
  - Stage 1 pure fetal HB cured by surgical resection alone
  - Only 1/3 to 1/2 have resectable disease at presentation
  - Preoperative chemotherapy converts > 50% of inoperable tumors to resectable tumors
  - Children's Oncology Group (COG) standard regimen consists of cisplatin, 5-fluorouracil, and vincristine (C5V)
- Liver transplant considered in unresectable cases

COG Staging System (Pretreatment Staging)

- Stage I: Completely resected tumor with negative margin
  - Stage II: Grossly resected tumor with microscopic residual tumor (positive margin)
  - Stage III: Unresectable tumor

- Biopsy diagnosis, partially resected, macroscopic residual tumor, tumor rupture
- Positive abdominal lymph node
- Stage IV: Metastasis to lungs, other organs, or sites distant from abdomen

Prognosis

- Tumor stage is key prognostic factor in survival
  - 90% event-free survival with complete tumor resection
  - < 70% event-free survival with nonmetastatic, unresectable tumor

Metastasis

- 10-20% of patients have metastases at presentation
- Lung most frequent, but can involve bone, brain, eye, or ovaries
- 20-30% survival with metastatic disease at presentation

Conditions Associated With HB

- Familial adenomatous polyposis, Beckwith-Wiedemann, Li-Fraumeni, Simpson-Golabi-Behmel syndromes
- Trisomy 18, glycogen storage disease types I-IV, hemihypertrophy

IMAGING

Radiographic Findings

- Solitary or multifocal mass
  - Heterogeneous and hypervascular
  - Calcification is common

Pretreatment Extent of Disease and Posttreatment Extent of Disease Classification

- Assessment made prior to or after chemotherapy
  - Guides surgical approach
  - Determines number of affected liver segments and extent of venous involvement
  - Pretreatment extent of disease (PRETEXT) guides surgical approach
  - I: 3 contiguous sections tumor free
  - II: 2 contiguous sections tumor free
  - III: 1 contiguous section tumor free
  - IV: No contiguous sections tumor free
  - Any group may have VPEMC component: V (ingrowth vena cava, all 3 hepatic veins), P (ingrowth portal vein, portal bifurcation), E (extrahepatic spread), M (metastasis), C (caudate lobe involvement)
- Indicators of poor prognosis: PRETEXT category IV, metastasis at diagnosis, small undifferentiated histology, AFP < 100 at diagnosis

MACROSCOPIC

General Features

- Solitary or multifocal, lobulated, heterogeneous mass
  - Fetal pattern areas resemble normal liver
  - Embryonal, small cell patterns: Softer, fleshy to gelatinous, gray-tan or pale pink
  - Mesenchymal: Osteoid-like areas firm or calcified
  - Teratoid, melanotic component: Dark brown or black
- Carefully search for vascular invasion

Size

- Large; can be > 15 cm

MICROSCOPIC

Histologic Features

- Epithelial patterns
  - Fetal
    - Uniform cells forming slender cords and trabeculae
    - Smaller than normal hepatocytes
    - Central round to oval nuclei, inconspicuous nucleolus, abundant clear to pink cytoplasm, distinct membrane
    - Alternating light and dark areas based on cytoplasmic glycogen content; may have fat
    - Low mitotic index (≤ 2 mitoses/10 HPF)
  - Crowded fetal (fetal with mitoses)
    - Similar to pure fetal, but for closely packed cells and higher mitoses (≥ 2 mitoses/10 HPF)
    - Slightly increased nuclear:cytoplasmic ratio
    - Intermixed with pure fetal pattern and merges into embryonal pattern; can be difficult to differentiate
  - Embryonal
    - Primitive cells in sheets, pseudorosettes, acini, tubules
    - Small, angulated nuclei (larger than fetal nuclei), coarse chromatin, prominent nucleoli, scant cytoplasm, indistinct membranes
    - Mitotic figures more frequent
  - Small undifferentiated
    - Can be difficult to recognize

– Resembles cells found in small round blue cell neoplasms
– Grows in sheets, infiltrative, lacks cohesion
– High nuclear to cytoplasmic ratio with almost no cytoplasm, hyperchromatic nuclei, inconspicuous nucleoli
– Can have rhabdoid-like cells with eccentric cytoplasm
– Variable mitotic rate

○ Extramedullary hematopoiesis in fetal and embryonal patterns
– Not useful to distinguish these epithelial patterns based on this finding alone

- Mesenchymal component
  - ○ Highly cellular primitive mesenchyme (immature spindle cells), scant cytoplasm, elongated plump nuclei
  - ○ Loose collagenous stroma &/or mature fibrous tissue
  - ○ Osteoid-like areas
    - – Immunoreactive for cytokeratin and EMA
  - ○ Bone, cartilage, and rhabdomyoblasts can be present
- Teratoid component
  - ○ Primitive neuroglia, ganglion cells, or melanin pigment
  - ○ Can also show bone, cartilage, rhabdomyoblasts, squamous cells, and mucinous glands

Morphologic Classification

- Epithelial HB (majority of HBs)
  - ○ Embryonal subtype alone or with fetal component
  - – Squamous epithelium and mucinous glands can be part of epithelial HB

○ Pure fetal histology HB
– 100% fetal pattern, no crowded fetal
– Low mitotic index (≤ 2 mitoses/10 HPF)

○ Macrotrabecular HB
– Fetal &/or embryonal cells in >10 cell-thick trabeculae

○ Small undifferentiated or small cell anaplastic HB
– > 70% of tumor is composed of small undifferentiated cells
– Any amount should be reported as percentage
– May be located toward center of embryonal region

- Mixed HB
  - ○ Both epithelial and mesenchymal elements
- Mixed HB with teratoid (heterologous) features
- Cholangioblastic

- Ductular differentiation at the periphery

Prognostic Factors

- Stage
  - Stage IV has uniform poor prognosis (39% 5-year survival)
- Histology
  - Pure fetal has excellent prognosis (100% 5-year, event-free survival)
  - Poor prognosis: Any small cell undifferentiated component, macrotrabecular HB
- α-fetoprotein < 100 confers worse prognosis

ANCILLARY TESTS

Immunohistochemistry

- Nuclear β-catenin staining in epithelial and mesenchymal components (70% of HB)
  - Nuclear staining not seen in most fetal HB
  - Positive in small undifferentiated cells
- Glypican-3 and Hep-Par1 positive in fetal and embryonal pattern
- Positive glutamine synthetase in fetal, variable in embryonal; both negative in small undifferentiated HB
- INI1/BAF47 loss in some small undifferentiated cells, especially if rhabdoid phenotype

DIFFERENTIAL DIAGNOSIS

Normal Liver Parenchyma

- Must distinguish fetal pattern from normal hepatocytes, particularly near margin
  - Nuclear &/or cytoplasmic β-catenin staining in HB
  - Fetal cells are smaller than normal hepatocytes

Hepatocellular Carcinoma

- May be indistinguishable from macrotrabecular HB
  - Biphasic pattern with fetal and embryonal cells in HB
  - Nuclear β-catenin, glypican-3 more often positive in HB
  - Nuclear inclusions, atypical mitoses and α-1-antitrypsin globules favor hepatocellular carcinoma

Teratoma

- Mature hepatocytes, lacks embryonal and fetal patterns
- No nuclear staining with β-catenin

Small Round Cell Tumors

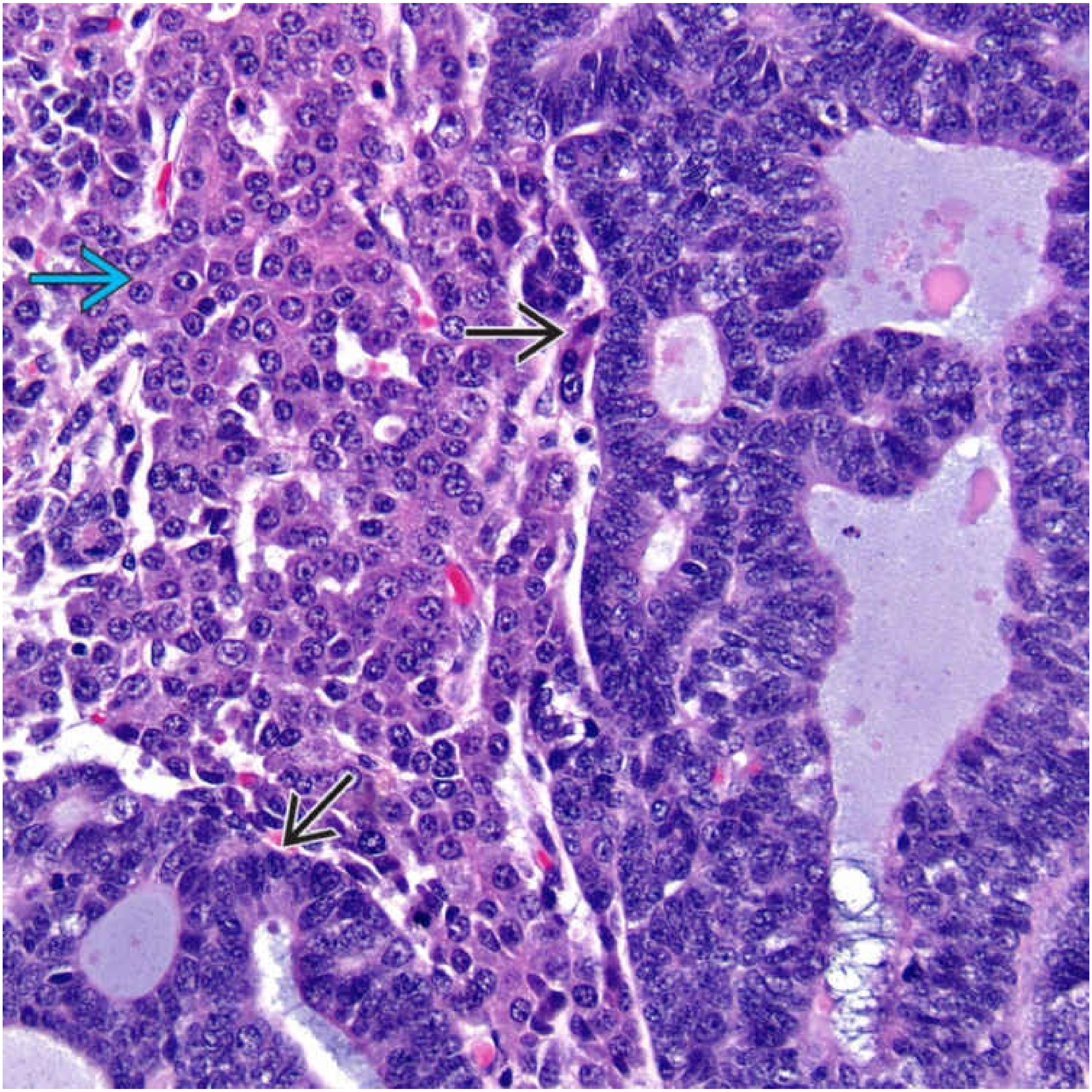
- Small undifferentiated HB may mimic metastatic small round cell tumors

    - Metastatic neuroblastoma, peripheral neuroectodermal tumor, Wilms tumor
- Clinical setting, morphology, and immunohistochemistry enables differentiation in most cases

DIAGNOSTIC CHECKLIST

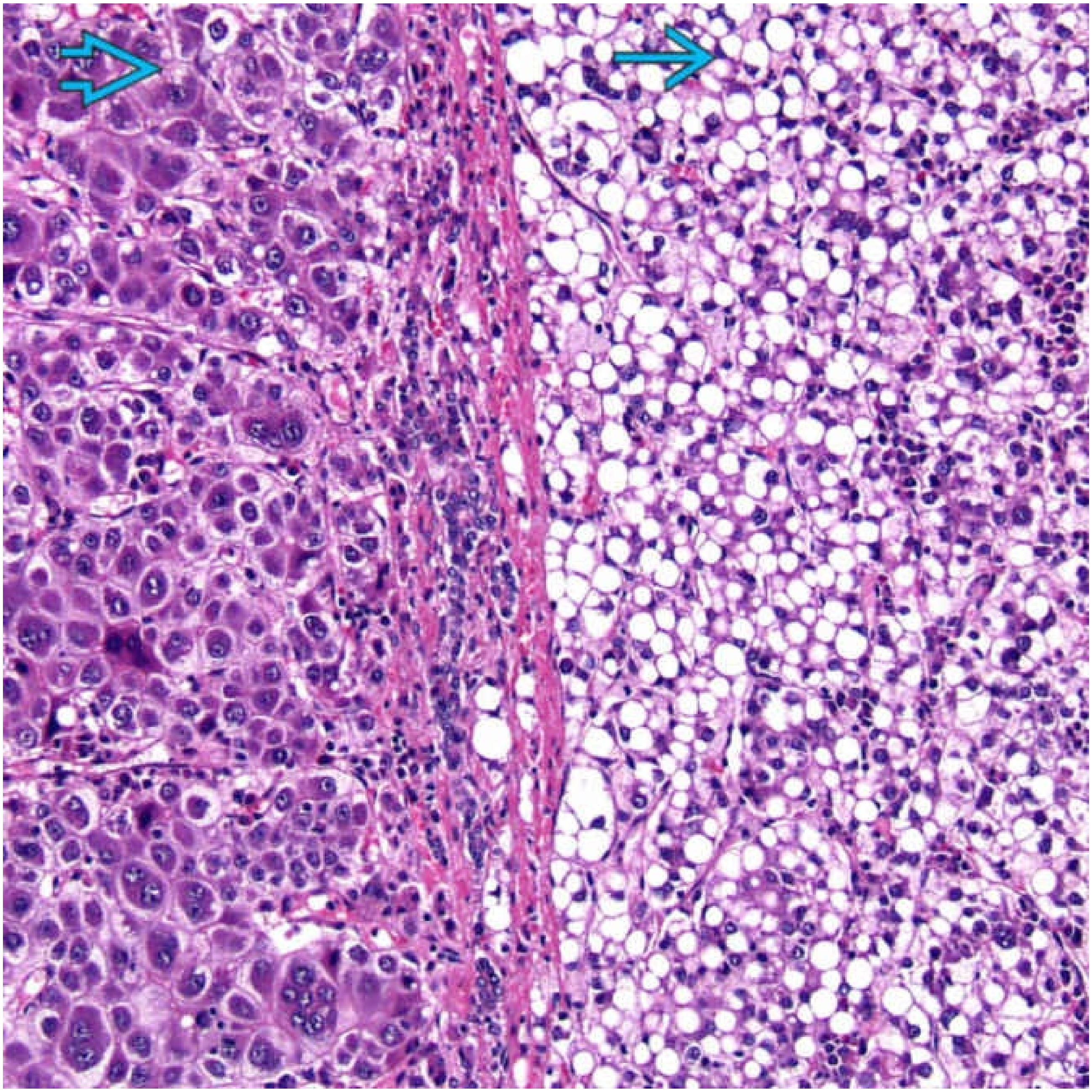
Clinically Relevant Pathologic Features

- Stage 1 pure fetal HB cured by surgical resection alone
- Important to report any amount of small undifferentiated cells; confers worse prognosis

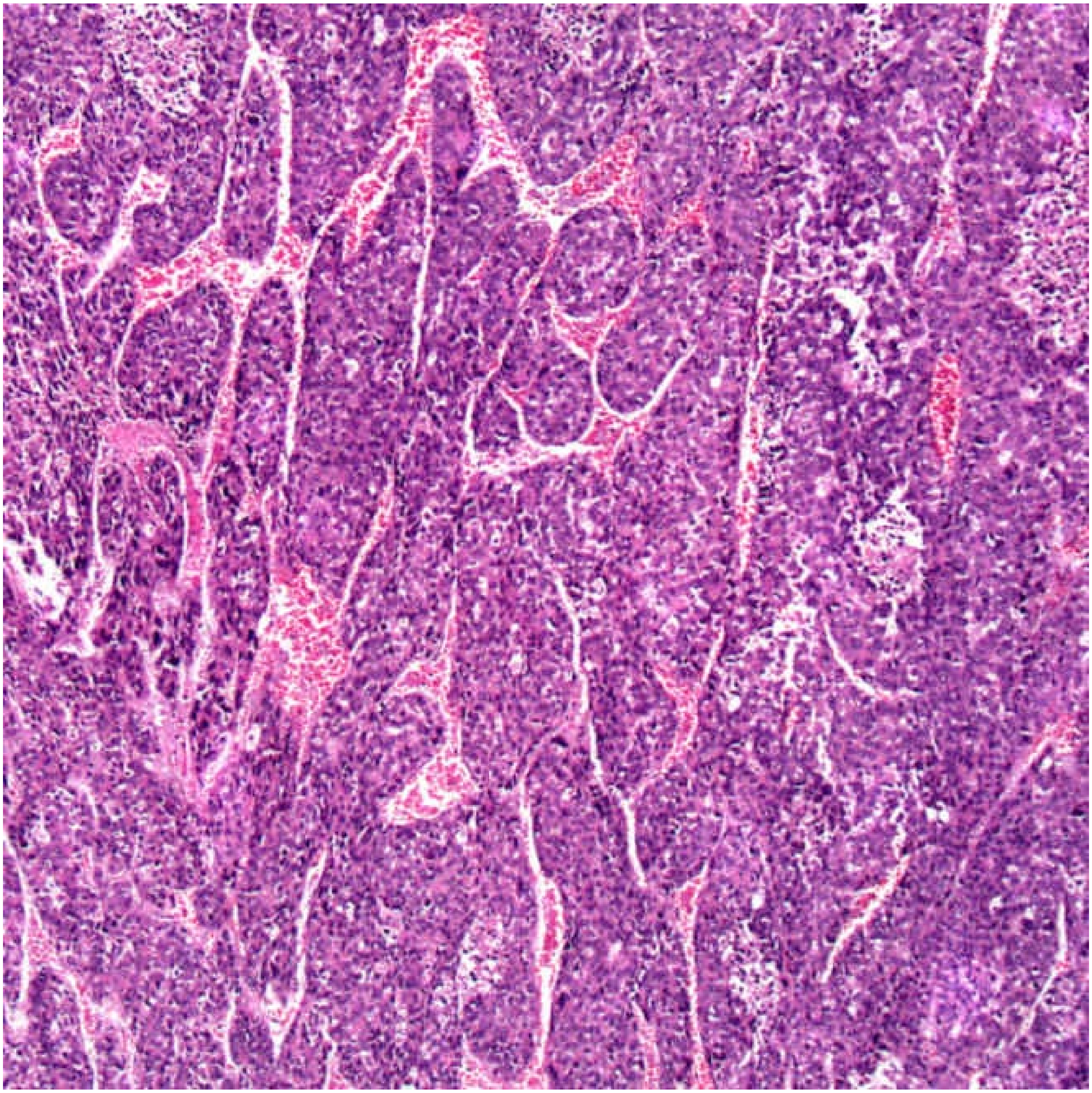


Embryonal Pattern

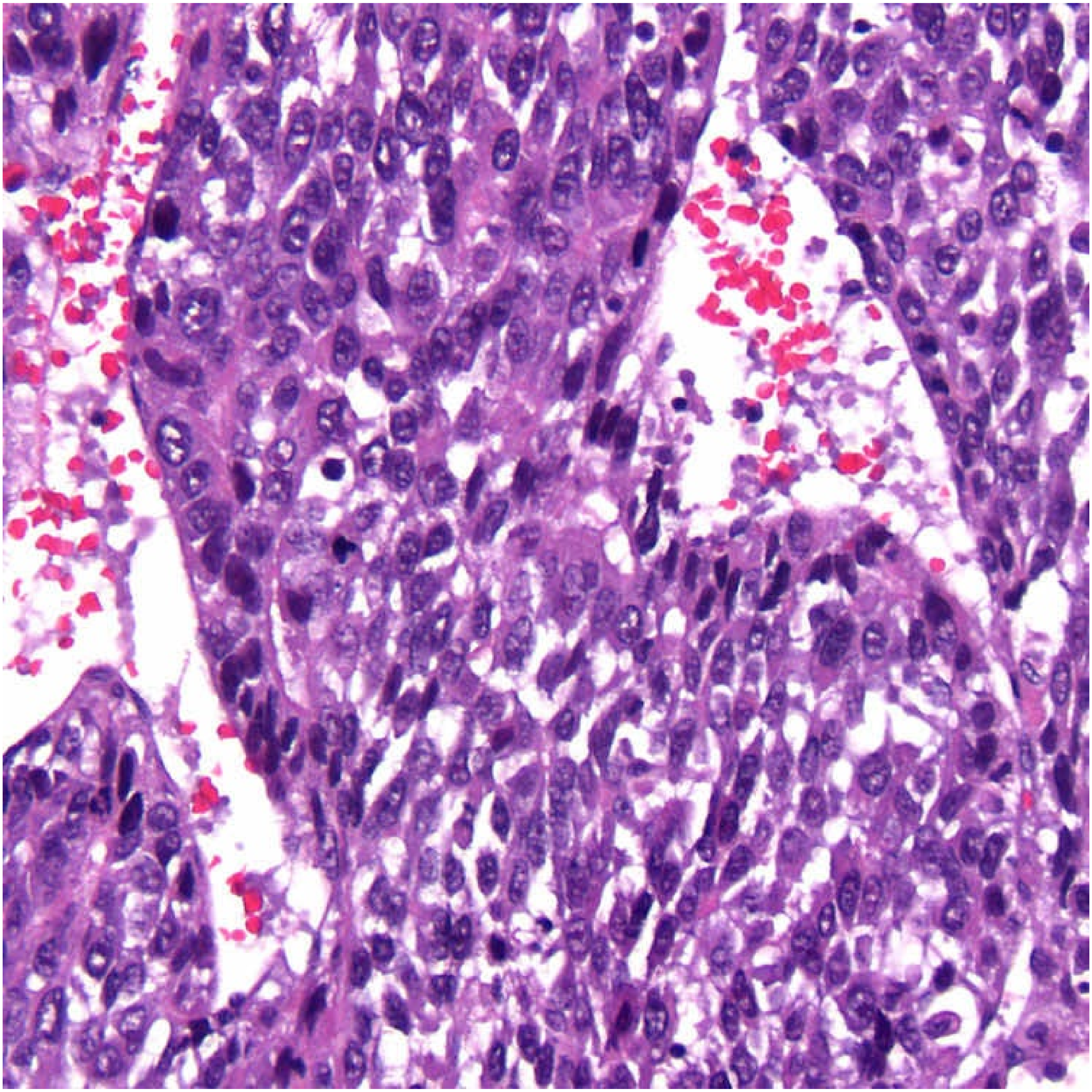
The embryonal epithelial cells are smaller and resemble small blue cell tumors. These cells can be arranged in a glandular structures →. Fetal pattern is also present → .



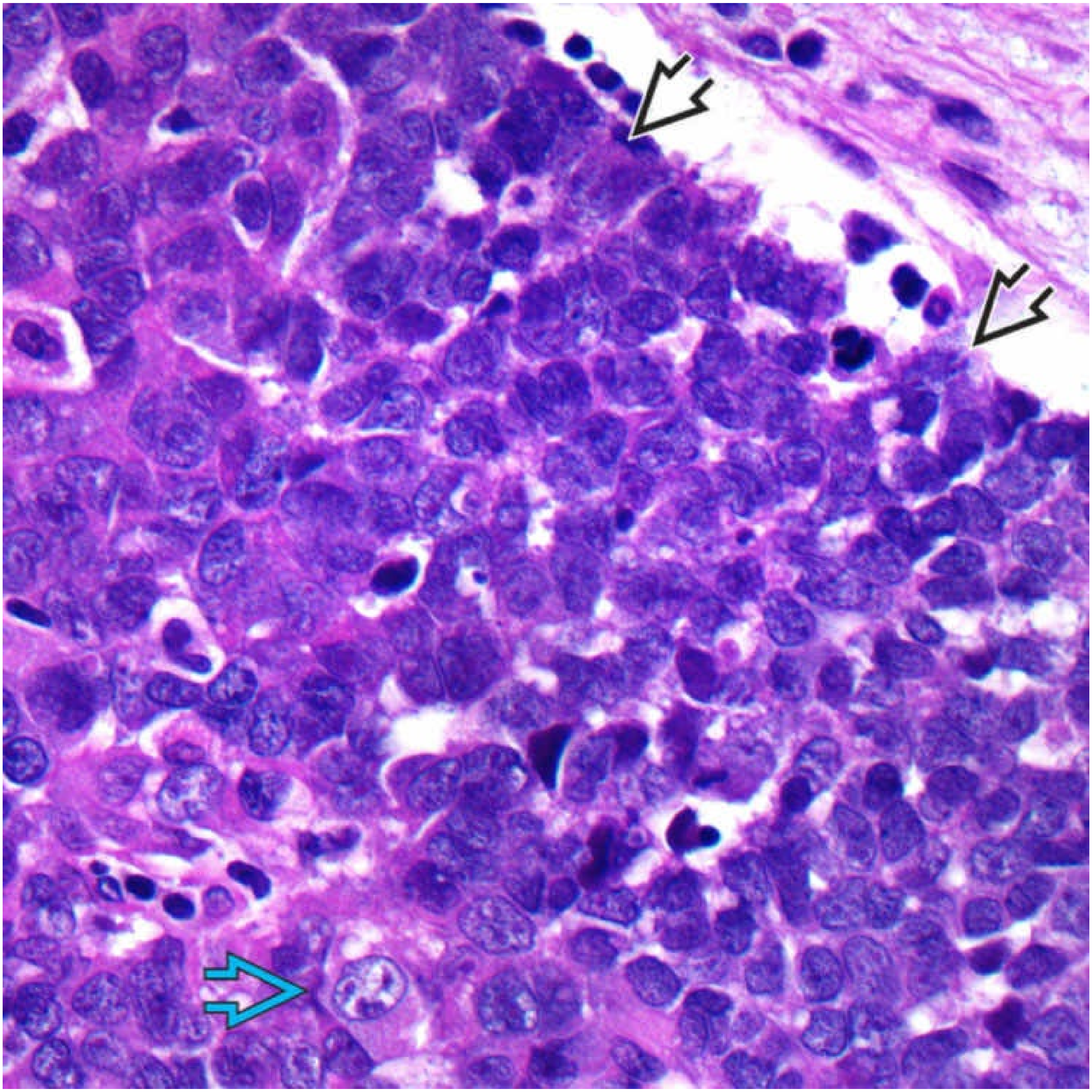
Crowded Fetal and Fetal Patterns
Epithelial hepatoblastoma (HB) with crowded fetal ➩ and fetal → patterns. Both have cytologically bland nuclei and abundant cytoplasm. Fat is seen in the fetal component.



Macrotrabecular Pattern
Macrotrabecular HB is composed of > 10-cells-thick trabeculae and can mimic hepatocellular carcinoma. Embryonal or mesenchymal components can assist in the diagnosis when present.

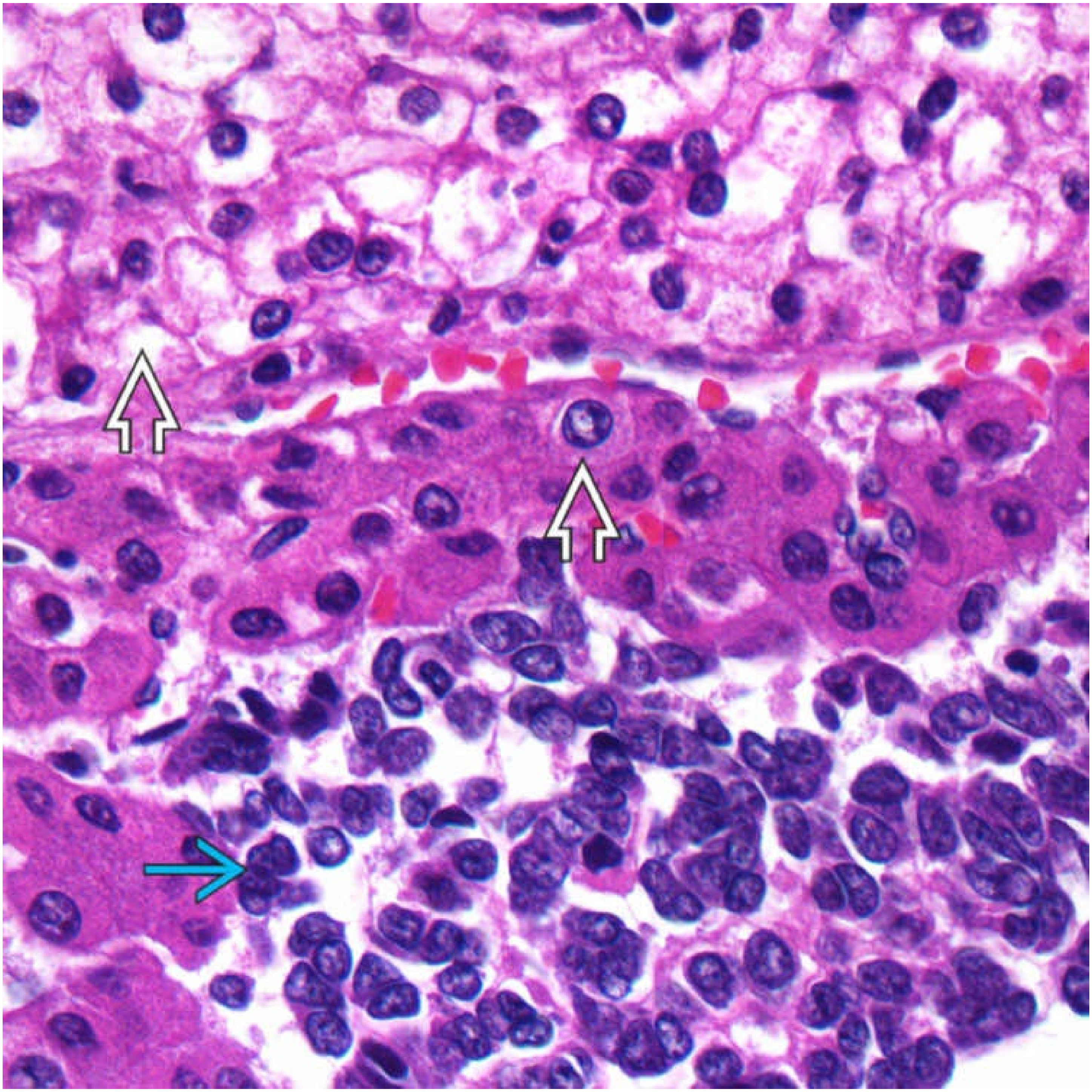


Macrotrabecular Pattern
H&E shows embryonal epithelial cells arranged in trabeculae > 10 cells thick, mimicking hepatocellular carcinoma.



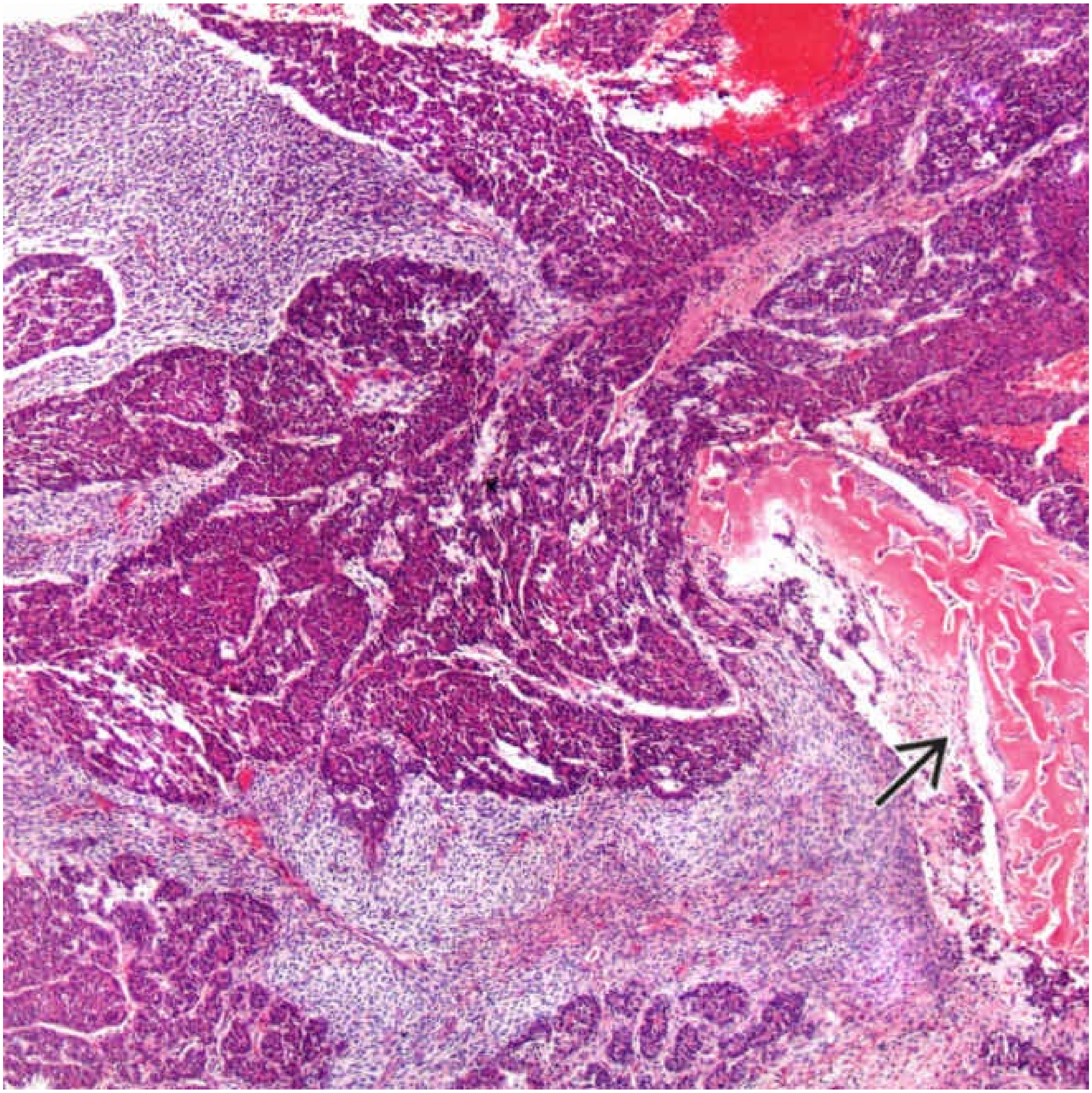
Small Undifferentiated Pattern

Embryonal epithelial cells ⇨ merge into a focus of small undifferentiated cells ⇨. The latter have even less cytoplasm and are often dyscohesive. These cells look like neuroblasts or blastemal cells but have positive nuclear stain for β-catenin. Even a microscopic focus of small undifferentiated cells confers a poorer prognosis.

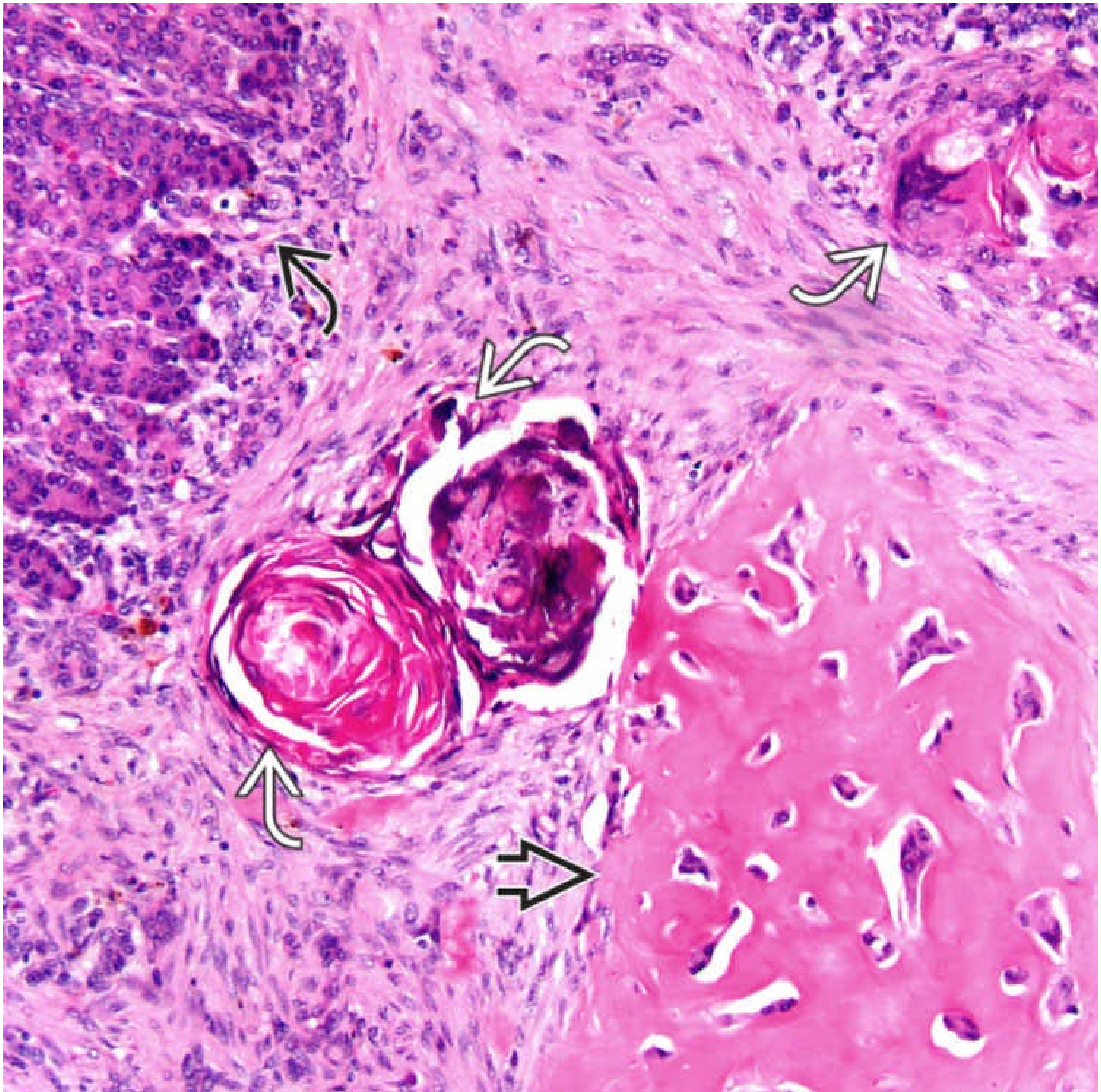


Small Undifferentiated Pattern

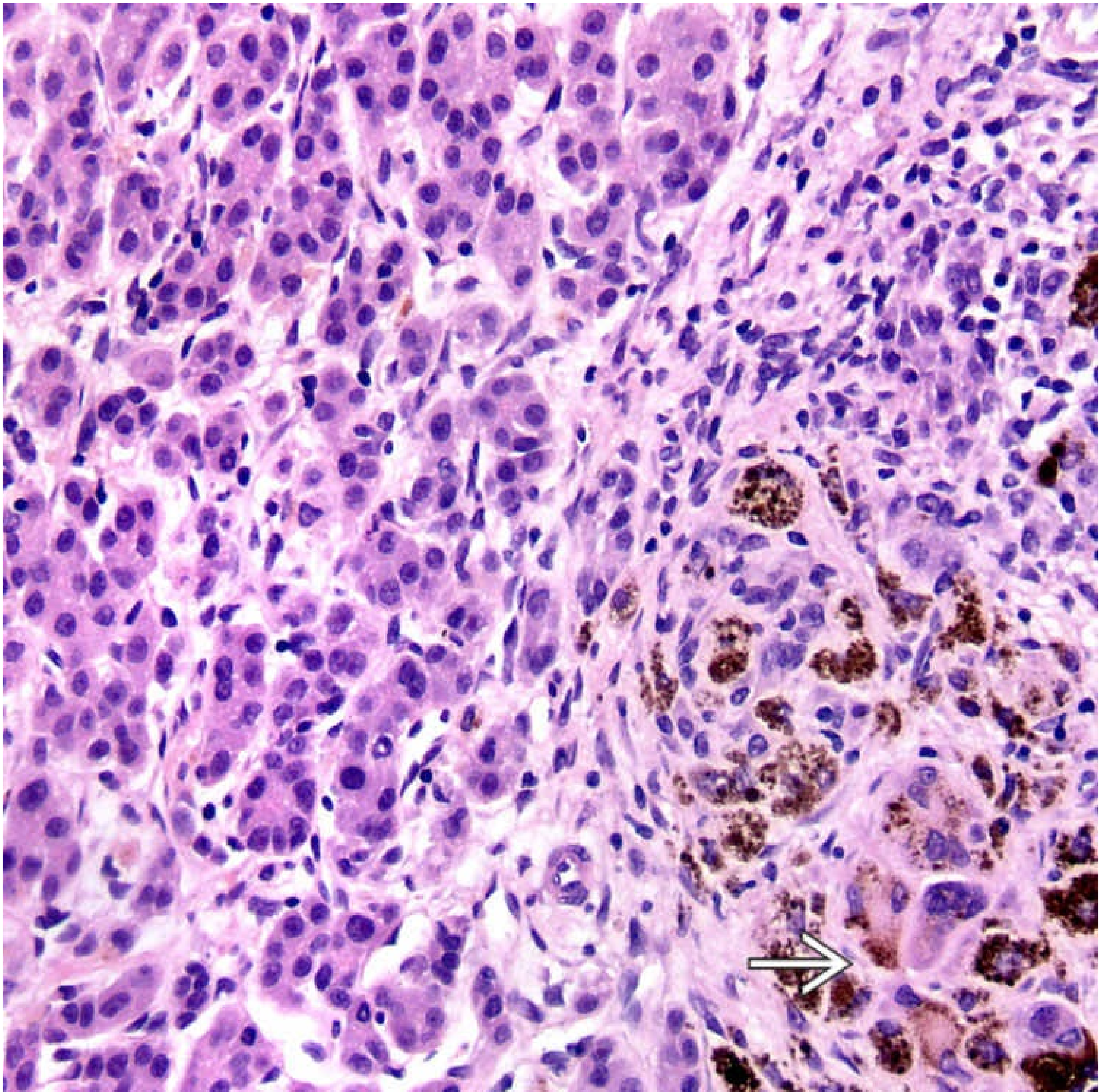
The amount of small undifferentiated component should be reported. In contrast, the fetal epithelial cells above have abundant cytoplasm with a variable amount of glycogen.



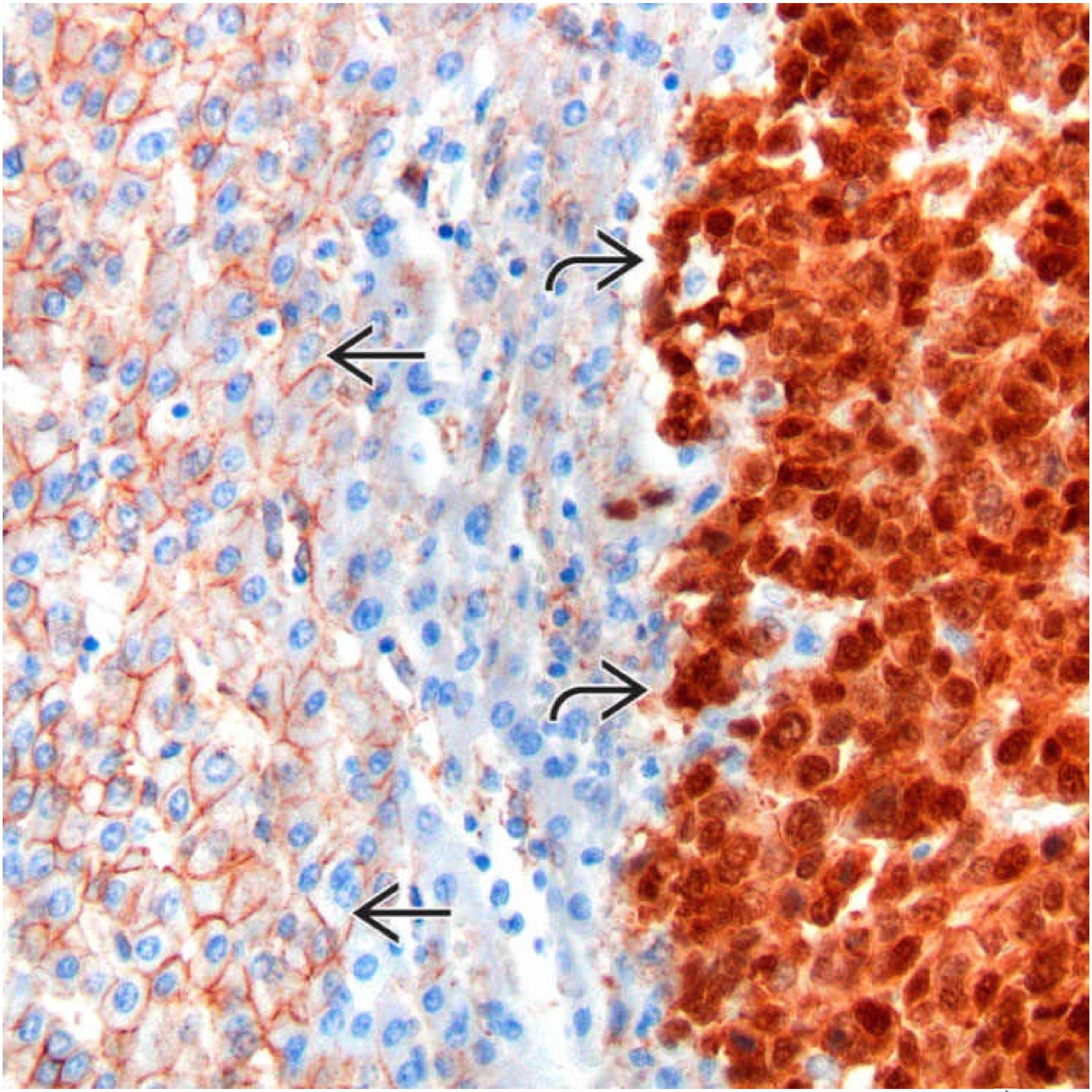
H&E shows mixed histologic patterns comprising embryonal epithelial cells, spindled mesenchymal component, and a focus of osteoid-like material →.



This mixed HB has neoplastic epithelial cells in cords, squamoid nests in dense fibrous stroma, and an osteoid-like focus. This is not considered a mixed HB with teratoid features because there is no neural or neuroectodermal differentiation.



Neoplastic epithelial cells are adjacent to ganglion-like cells ⇒ that have brown melanin pigment in this mixed epithelial and mesenchymal hepatoblastoma with teratoid features.



Diffuse and strong nuclear and cytoplasmic staining is shown in neoplastic cells in hepatoblastoma ↷.
The normal hepatocytes → show membranous staining without nuclear staining.

SELECTED REFERENCES

1. Kremer, N, et al. Management of hepatoblastoma: an update. *Curr Opin Pediatr*. 2014; 26(3):362–369.
2. López-Terrada, D, et al. Towards an international pediatric liver tumor consensus classification: proceedings of the Los Angeles COG liver tumors symposium. *Mod Pathol*. 2014; 27(3):472–491.
3. Meyers, RL, et al. Liver transplantation in the management of unresectable hepatoblastoma in children. *Front Biosci (Elite Ed)*. 2012; 4:1293–1302.

4. Wang, LL, et al. Effects of neoadjuvant chemotherapy on hepatoblastoma: a morphologic and immunohistochemical study. *Am J Surg Pathol*. 2010; 34(3):287–299.
5. Meyers, RL, et al. Predictive power of pretreatment prognostic factors in children with hepatoblastoma: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2009; 53(6):1016–1022.
6. Finegold, MJ, et al. Protocol for the examination of specimens from pediatric patients with hepatoblastoma. *Arch Pathol Lab Med*. 2007; 131(4):520–529.
7. Rowland, JM. Hepatoblastoma: assessment of criteria for histologic classification. *Med Pediatr Oncol*. 2002; 39(5):478–483.
8. Stocker, JT. Hepatic tumors in children. *Clin Liver Dis*. 2001; 5(1):259–281. [viii-ix].

Bile Duct Adenoma

KEY FACTS

Terminology

- Historically called “bile duct adenoma” but shown to have phenotype of peribiliary glands rather than bile ducts

Etiology/Pathogenesis

- *BRAF* V600E mutations in > 50% of cases

Clinical Issues

- Almost always incidental finding during surgery for another reason
  - Often submitted for frozen section to rule out metastasis

Microscopic

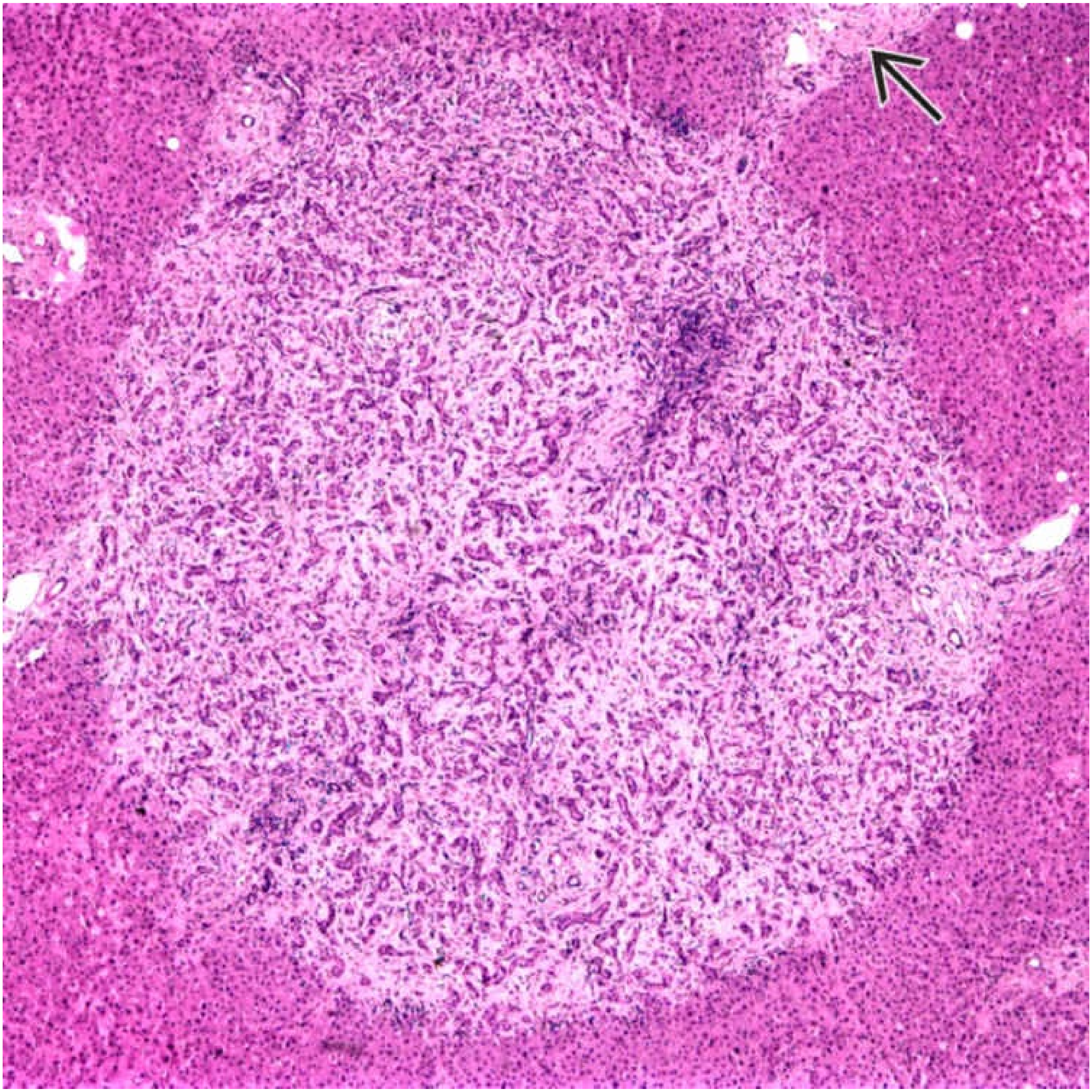
- Uniformly sized tubules and acini with rounded outlines
- Single layer of cuboidal to columnar cells that lack atypia, hyperchromasia, mitoses
- Fibrous stroma either scant or dense and hyalinized
- Bile is not present, and ducts do not communicate with biliary tree
- Variant features include clear cell change, mucinous metaplasia, neuroendocrine differentiation, and α-1-antitrypsin globules
- Circumscribed outline and lack of cytologic atypia are most important features to distinguish from adenocarcinoma

Ancillary Tests

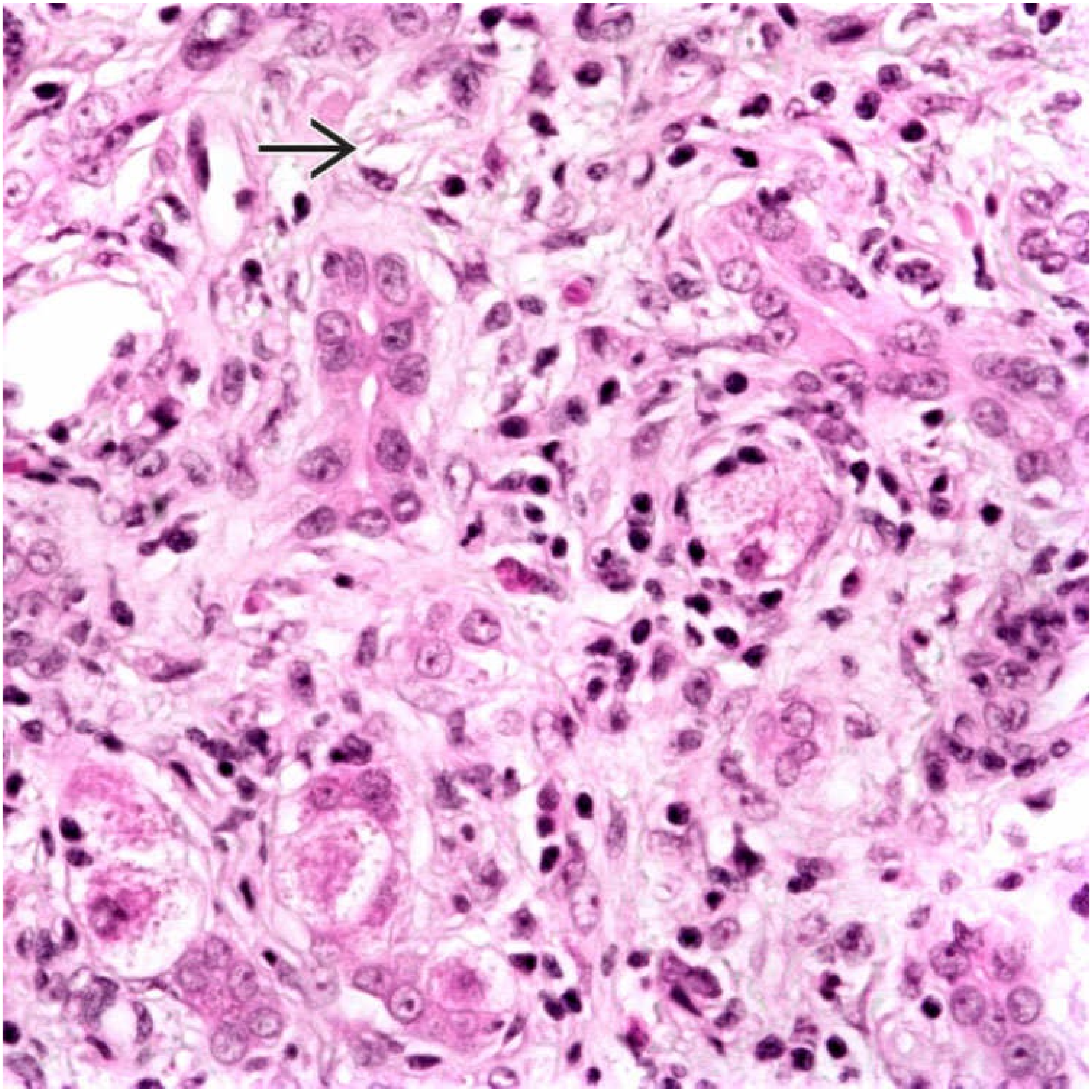
- Ki-67 typically < 10%
- p53 weak and patchy
- DPC4 is intact in contrast to most of metastatic pancreatic ductal adenocarcinomas

Top Differential Diagnoses

- Biliary microhamartoma (von Meyenburg complex)
- Intrahepatic cholangiocarcinoma
- Metastatic adenocarcinoma
- Neuroendocrine tumor

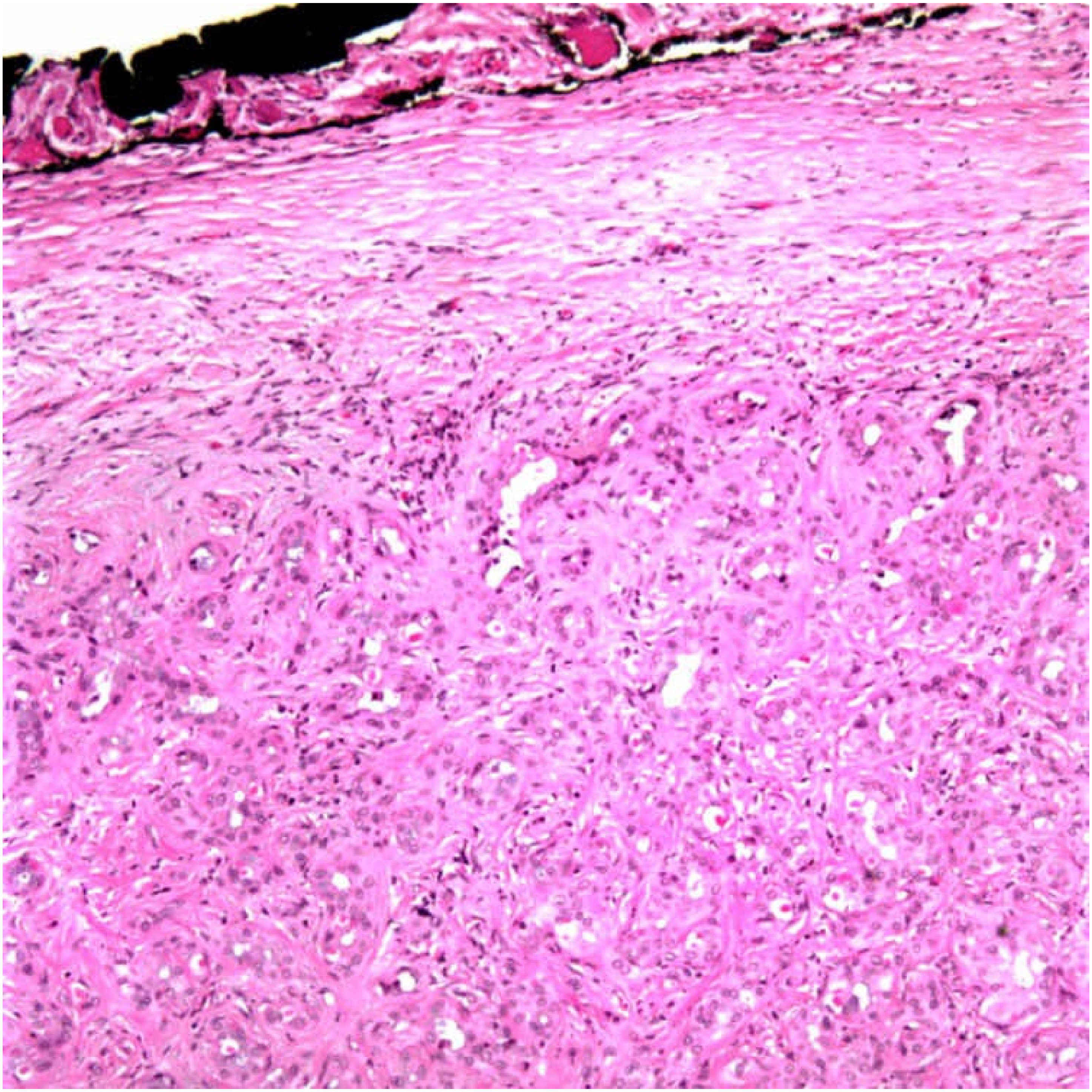


Well-Circumscribed Lesion
Bile duct adenomas are well circumscribed but unencapsulated. Note the fibrous stroma and evenly distributed glands. An adjacent normal portal tract → is present.

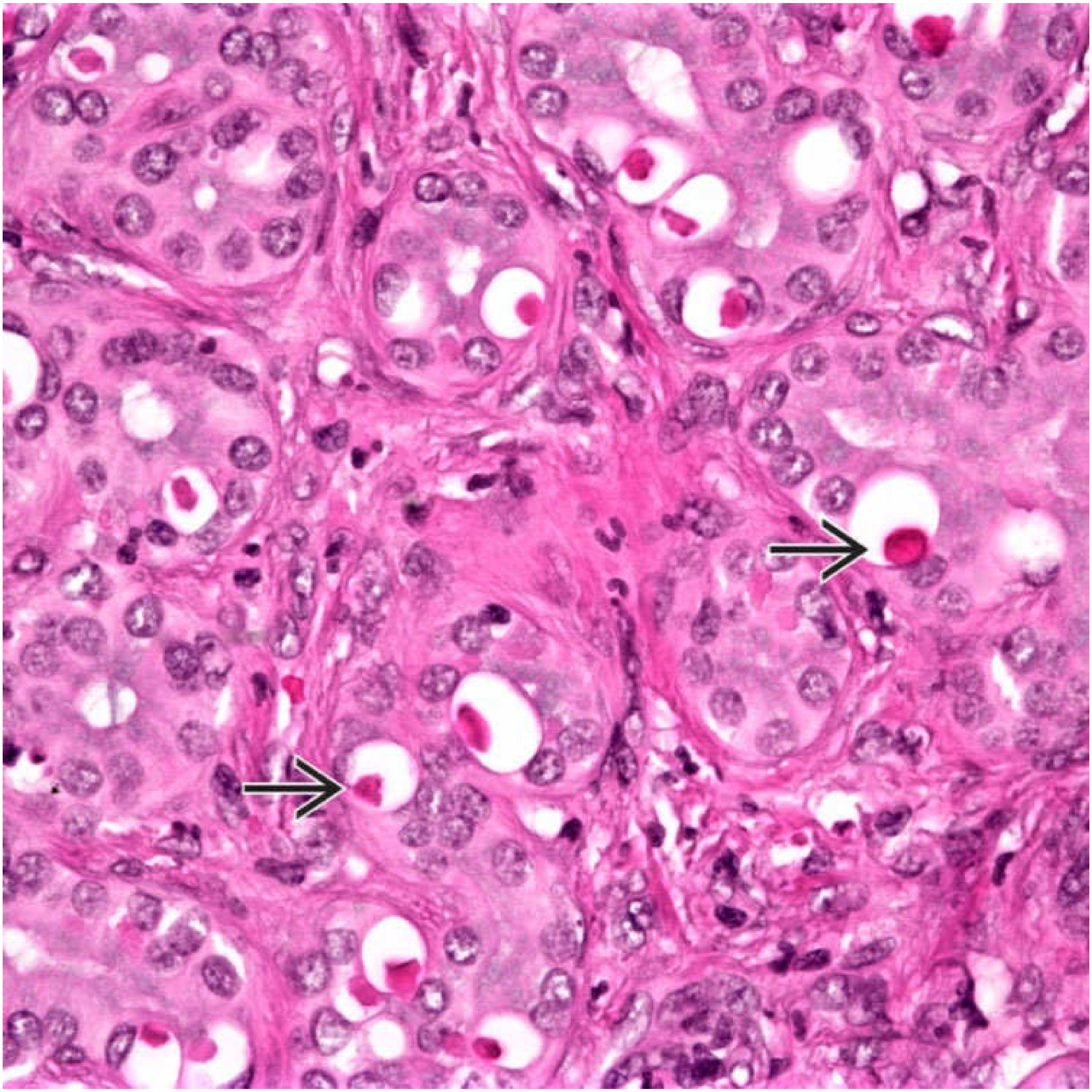


Loose Fibrous Stroma

Most bile duct adenomas have a scant compact stroma, while others may show abundant loose fibrous stroma with admixed chronic inflammation →. The stroma tends to be more prominent toward the center of the lesion. The tubular glands are lined by a single layer of cuboidal epithelium with uniform nuclei.



Subcapsular Location
Most bile duct adenomas are located in the subcapsular region. These are often noted intraoperatively during abdominal surgery and can mimic metastatic disease.



Cytoplasmic Globules

Some bile duct adenomas contain eosinophilic cytoplasmic globules composed of α-1-antitrypsin →. Note the lack of nuclear atypia, mitoses, or nuclear hyperchromasia in the lining epithelium of small rounded glands.

TERMINOLOGY

Abbreviations

- Bile duct adenoma (BDA)

Synonyms

- Bile duct adenoma, cholangioma, cholangioadenoma

Definitions

- Small, benign epithelial tumor composed of glands that resemble bile ducts

ETIOLOGY/PATHOGENESIS

Molecular Changes

- *BRAF* V600E mutations in > 50% of cases

CLINICAL ISSUES

Epidemiology

- Age
  - > 40 years
- Sex
  - Equal gender distribution

Presentation

- Almost always incidental findings during surgery for another reason
  - Often submitted for frozen section during intraabdominal surgery to exclude metastasis

Prognosis

- Excellent
  - Malignant transformation has not been well documented

MACROSCOPIC

General Features

- Typically small (< 1 cm), rarely up to 4 cm
- Usually single but can be multiple
- Well circumscribed but not encapsulated
- Often subcapsular
- Firm and gray-white

MICROSCOPIC

Histologic Features

- Uniformly sized tubules and acini
  - Single layer of cuboidal to columnar cells

- No cytoarchitectural atypia or mitoses
  - Small or inapparent lumina with rounded outlines
- Fibrous stroma either scant or dense and hyalinized
  - More abundant centrally than peripherally
- Variable amount of inflammation present
- Normal portal tracts &/or large bile ducts often associated with BDA
- Bile is not present
  - Ducts do not communicate with biliary tree
- Acidic mucin is usually present
- Variant features
  - Mucinous metaplasia
  - Neuroendocrine differentiation
  - α-1-antitrypsin globules
    - Rare cases associated with α-1-antitrypsin deficiency also contain α-1-antitrypsin globules
  - Rare variant with clear cells can be mistaken for primary or metastatic clear cell carcinoma

ANCILLARY TESTS

Immunohistochemistry

- Ki-67 typically < 10%, p53 weak and patchy
- DPC4 is intact

DIFFERENTIAL DIAGNOSIS

Biliary Microhamartoma (von Meyenburg Complex)

- Curvilinear and angular rather than round ducts
- More abundant stroma
- Often contain bile
- Associated with polycystic liver disease

Cholangiocarcinoma/Metastatic Adenocarcinoma

- Nuclear atypia
  - Poorly circumscribed
  - Infiltrative or destructive growth pattern
- Lymphovascular or perineural invasion
- Mitoses
- Bile duct adenomas are small (usually < 1 cm) and almost always found incidentally in asymptomatic patients
- Ki-67 often > 10%, DPC4 may be lost in metastatic pancreatic ductal adenocarcinoma

Neuroendocrine Tumor

- Endocrine cell clusters in some bile duct adenomas can be confused with metastatic neuroendocrine tumors

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Almost always incidental findings at time of surgery for another intraabdominal process
  - This lesion is most noteworthy for being mistaken for metastatic adenocarcinoma

SELECTED REFERENCES

1. Pujals, A, et al. BRAF V600E mutational status in bile duct adenomas and hamartomas. *Histopathology*. 2015; 67(4):562–567.
2. Hornick, JL, et al. Immunohistochemistry can help distinguish metastatic pancreatic adenocarcinomas from bile duct adenomas and hamartomas of the liver. *Am J Surg Pathol*. 2005; 29(3):381–389.
3. Albores-Saavedra, J, et al. Atypical bile duct adenoma, clear cell type: a previously undescribed tumor of the liver. *Am J Surg Pathol*. 2001; 25(7):956–960.
4. Bhathal, PS, et al. The so-called bile duct adenoma is a peribiliary gland hamartoma. *Am J Surg Pathol*. 1996; 20(7):858–864.
5. O'Hara, BJ, et al. Bile duct adenomas with endocrine component. Immunohistochemical study and comparison with conventional bile duct adenomas. *Am J Surg Pathol*. 1992; 16(1):21–25.
6. Allaire, GS, et al. Bile duct adenoma. A study of 152 cases. *Am J Surg Pathol*. 1988; 12(9):708–715.
7. Govindarajan, S, et al. The bile duct adenoma. A lesion distinct from Meyenburg complex. *Arch Pathol Lab Med*. 1984; 108(11):922–924.

von Meyenburg Complex (Biliary Microhamartoma)

KEY FACTS

Terminology

- Synonyms include
  - Ductal plate malformation
  - Biliary microhamartoma

Etiology/Pathogenesis

- Developmental malformation resulting from aberrant construction/remodeling of embryonic bile ducts
  - Majority are sporadic
  - Also associated with several fibropolycystic liver diseases

Clinical Issues

- Reportedly occurs in ~ 3% of autopsied patients
- Not considered premalignant

Macroscopic

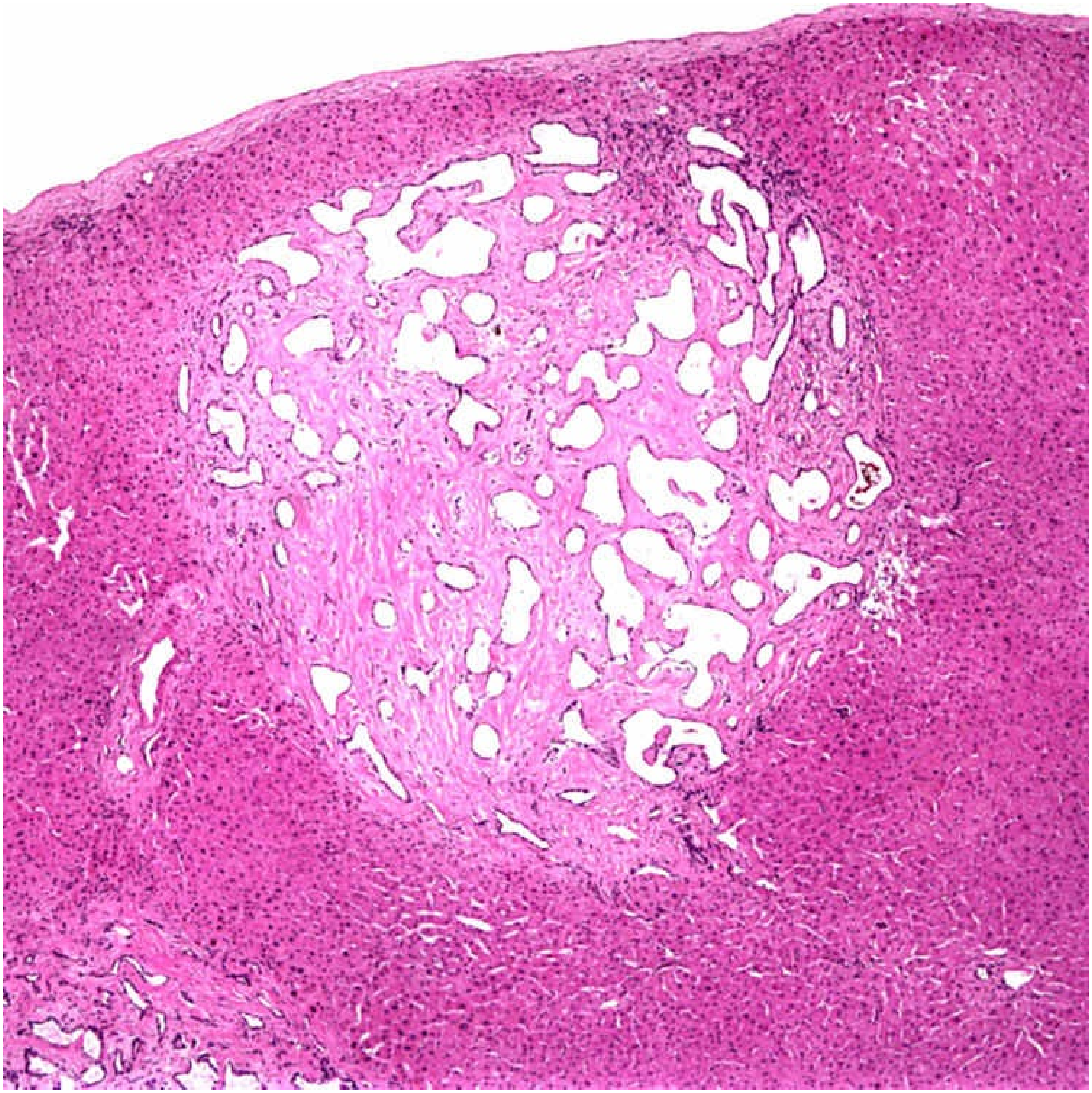
- Usually multifocal
- Often subcapsular
- Typically < 0.5 cm

Microscopic

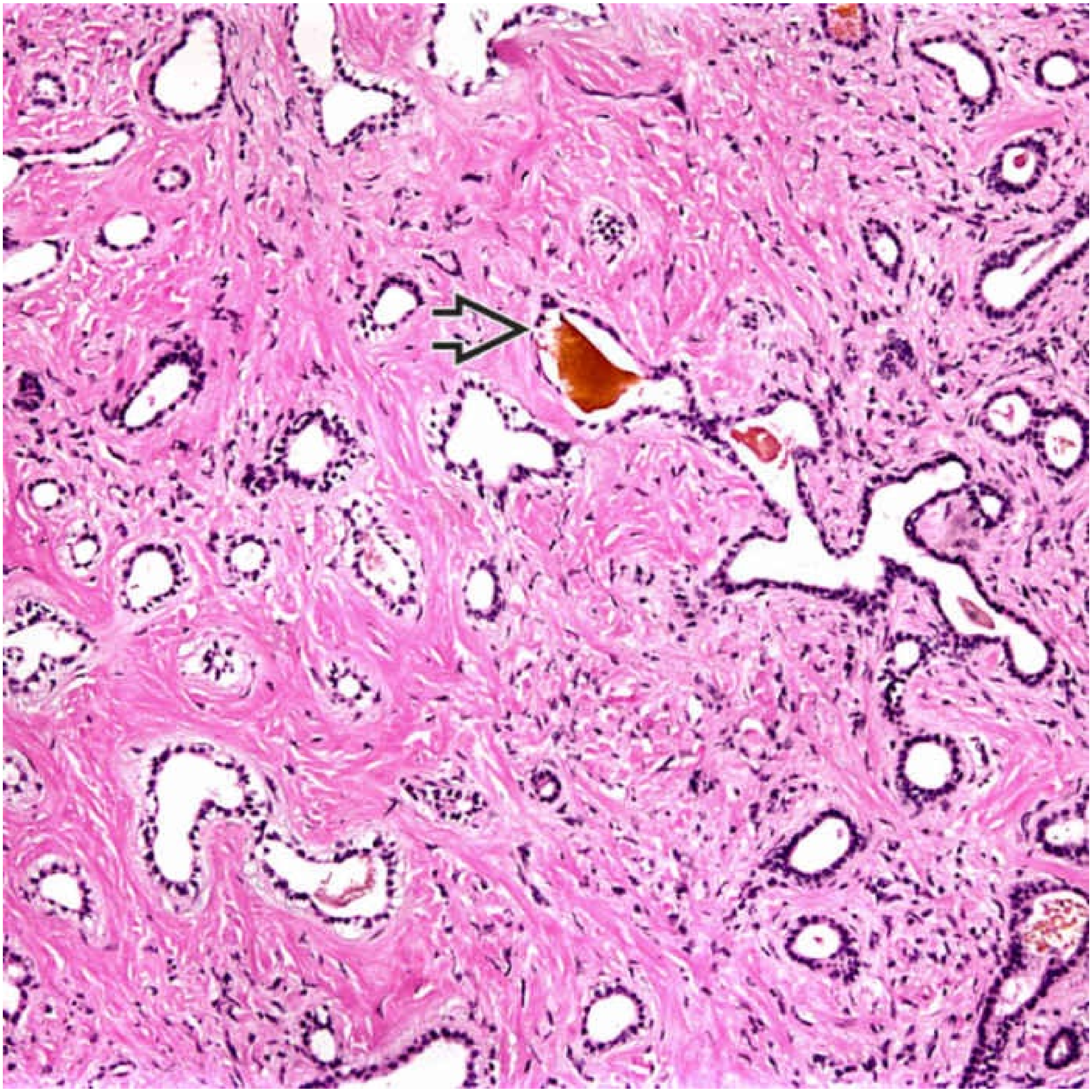
- Angulated, branching, irregular ducts embedded in dense fibrous stroma
  - Usually within or at edge of portal tracts
  - Ducts are lined by cuboidal, often flattened, epithelium
  - Ducts may contain eosinophilic proteinaceous debris or inspissated bile

Diagnostic Checklist

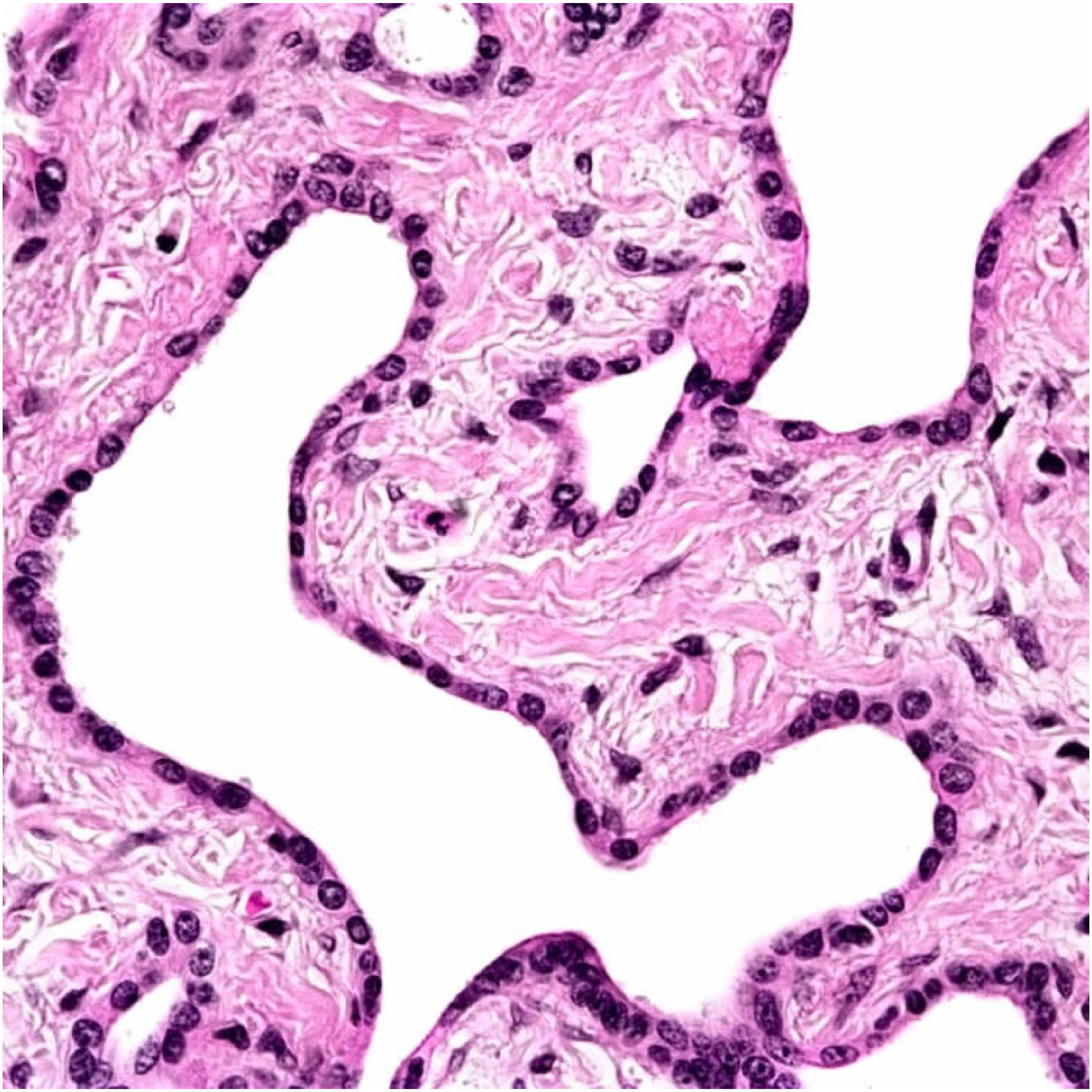
- Multiple widely scattered von Meyenburg complexes raise possibility of associated fibropolycystic disease
- May be submitted for frozen section during abdominal surgery to exclude liver metastasis



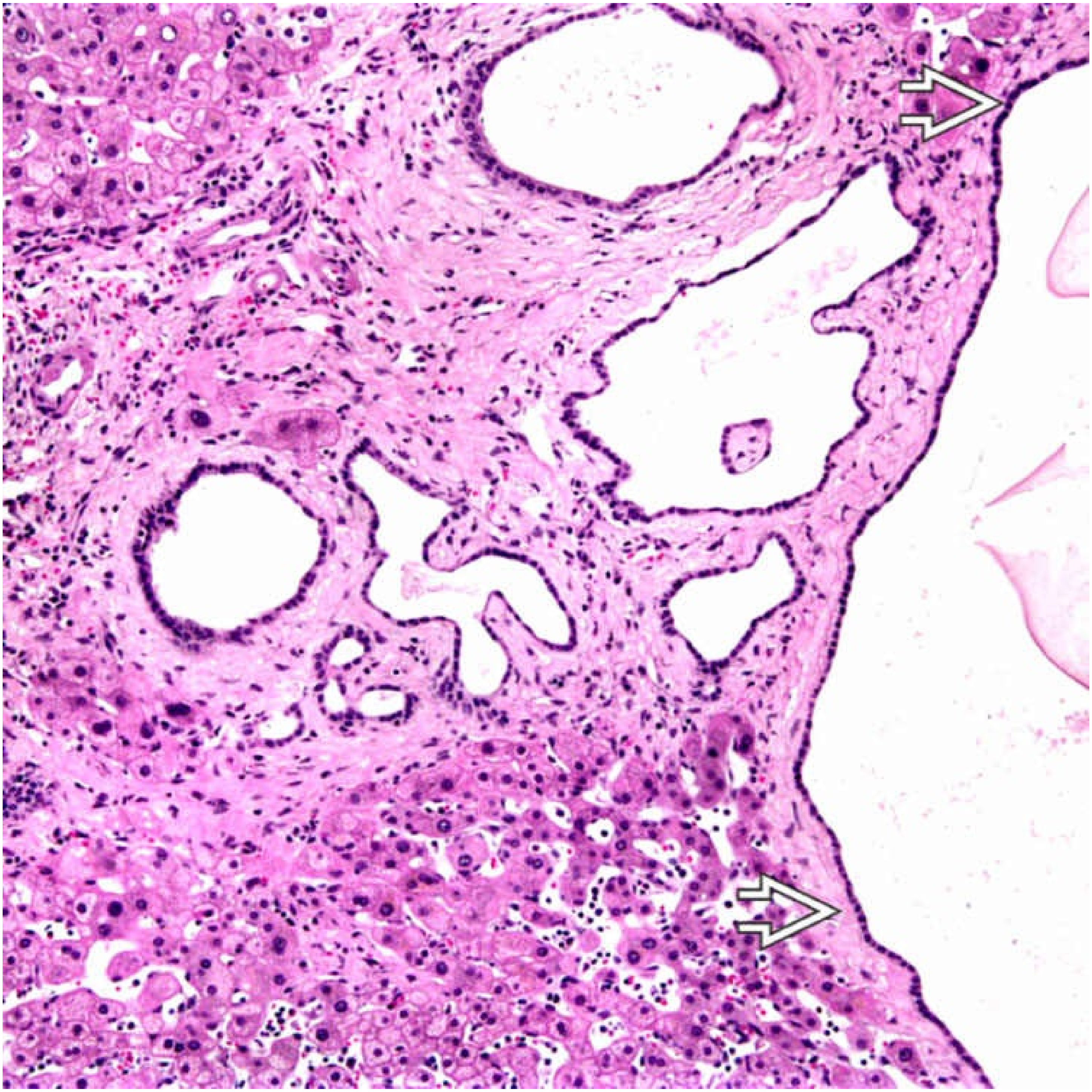
von Meyenburg Complex, Low Power
This small, subcapsular von Meyenburg complex (VMC) features branching, irregular, angulated glands embedded in dense fibrous stroma.



von Meyenburg Complex, Medium Power
VMC is characterized by angulated, branching glands within dense, fibrous stroma. Note the inspissated bile ⇨. There is no nuclear atypia and no mitoses.



von Meyenburg Complex, High Power
The branching, angulated glands in VMC are lined by a single layer of flattened cuboidal epithelium. There is no nuclear atypia.



von Meyenburg Complex and Polycystic Liver Disease
Some of the glands within VMC have dilated to produce a cyst, which is filled with eosinophilic proteinaceous material. This patient has autosomal dominant polycystic disease.

TERMINOLOGY

Abbreviations

- von Meyenburg complex (VMC)

Synonyms

- Biliary microhamartoma

- Ductal plate malformation

Definitions

- Developmental malformation resulting from aberrant construction/remodeling of embryonic bile ducts

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Most often sporadic
  - Also within spectrum of numerous fibropolycystic diseases of liver including congenital hepatic fibrosis, Caroli disease, autosomal dominant polycystic disease
  - Basic lesion of congenital hepatic fibrosis
  - Considered precursor lesion of autosomal dominant polycystic liver disease

CLINICAL ISSUES

Epidemiology

- Incidence
  - Not precisely known
  - Reportedly occurs in ~ 3% of autopsied patients

Presentation

- Often incidental findings at surgery or autopsy
  - May be submitted for frozen section during abdominal surgery to exclude metastasis

Treatment

- None for sporadic lesions
- Treat underlying disease if part of fibropolycystic disease

Prognosis

- Not considered premalignant
  - Rare cases of cholangiocarcinoma arising in VMC have been reported

MACROSCOPIC

General Features

- Majority are small (usually < 0.5 cm), gray-white, irregular, and commonly multifocal
  - Most often multiple
  - Can be solitary

- Presence of numerous, widely scattered VMC raises possibility of fibropolycystic disease or congenital hepatic fibrosis
- Gray-white or green
- Often subcapsular

MICROSCOPIC

Histologic Features

- Located within and at edge of portal tracts
  - Small- to medium-sized ducts embedded in dense fibrous stroma
  - Many ducts are irregularly shaped, angulated, or branching and dilated
  - – Ducts are lined by cuboidal, often flattened epithelium
  - – No atypia
  - – No mitotic activity
  - – Ducts may contain eosinophilic proteinaceous debris or inspissated bile
- Varying degrees of dilatation that may eventually lead to cyst formation
- Not connected to normal biliary tree
- Transition to dysplasia and cholangiocarcinoma has been very rarely noted

DIFFERENTIAL DIAGNOSIS

Bile Duct Adenoma

- Glands have uniform round outlines
  - Bile is absent
  - Absence of cystic changes
  - Not associated with fibropolycystic liver diseases
  - Immunohistochemistry
  - Bile duct adenoma expresses 1F6 and D10, similar to bile ductules and canals of Hering
  - VMC expresses D10, but not 1F6

Cholangiocarcinoma/Metastatic Adenocarcinoma

- Nuclear atypia, infiltrative or destructive growth pattern, mitoses
- Lymphovascular or perineural invasion

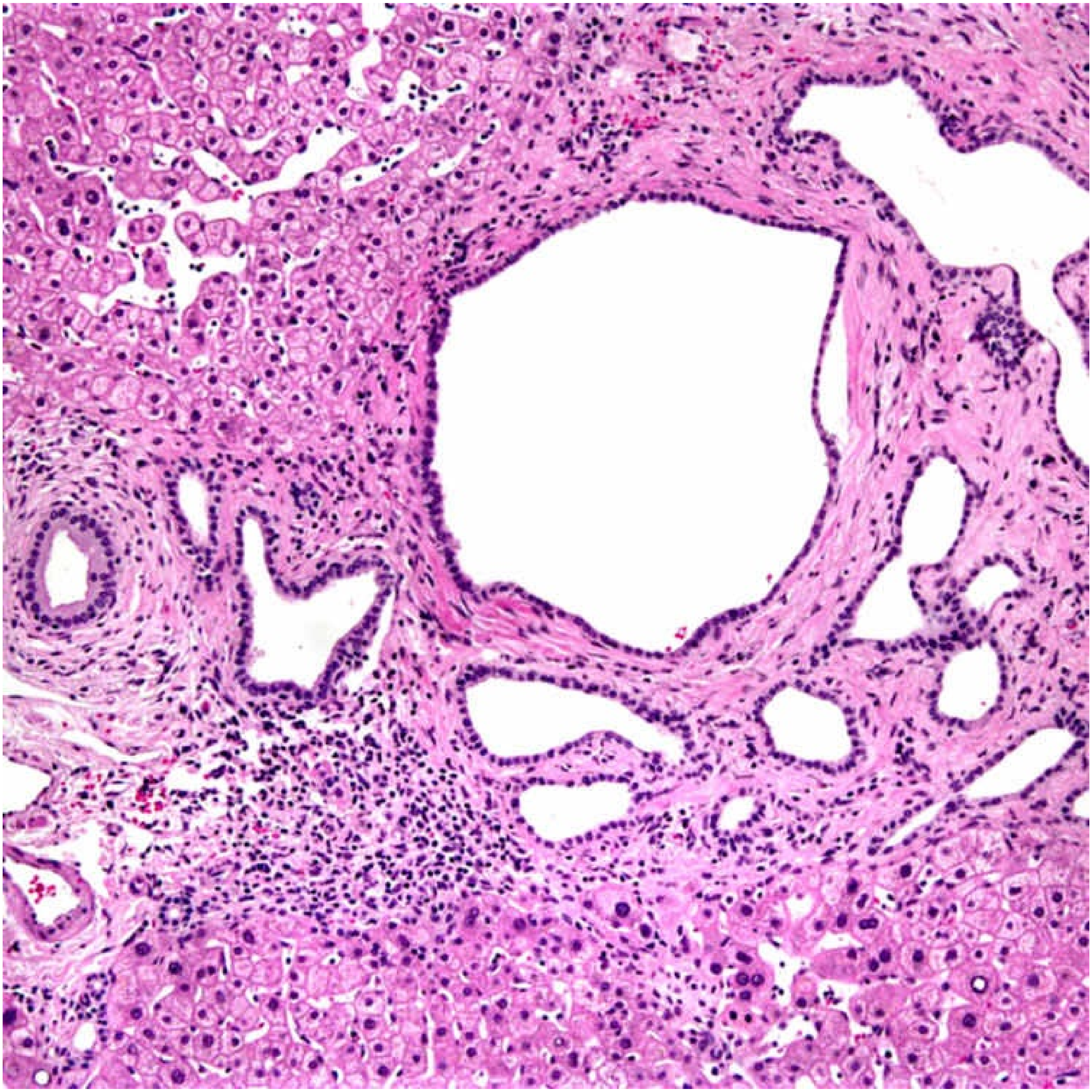
Biliary Adenofibroma

- Rare entity with few reported cases
  - Cystic and tubular duct elements with prominent fibroblastic stroma
  - Immunophenotype same as VMC
  - Bears marked resemblance to biliary hamartoma but larger
  - Does not appear to be associated with fibropolycystic liver diseases

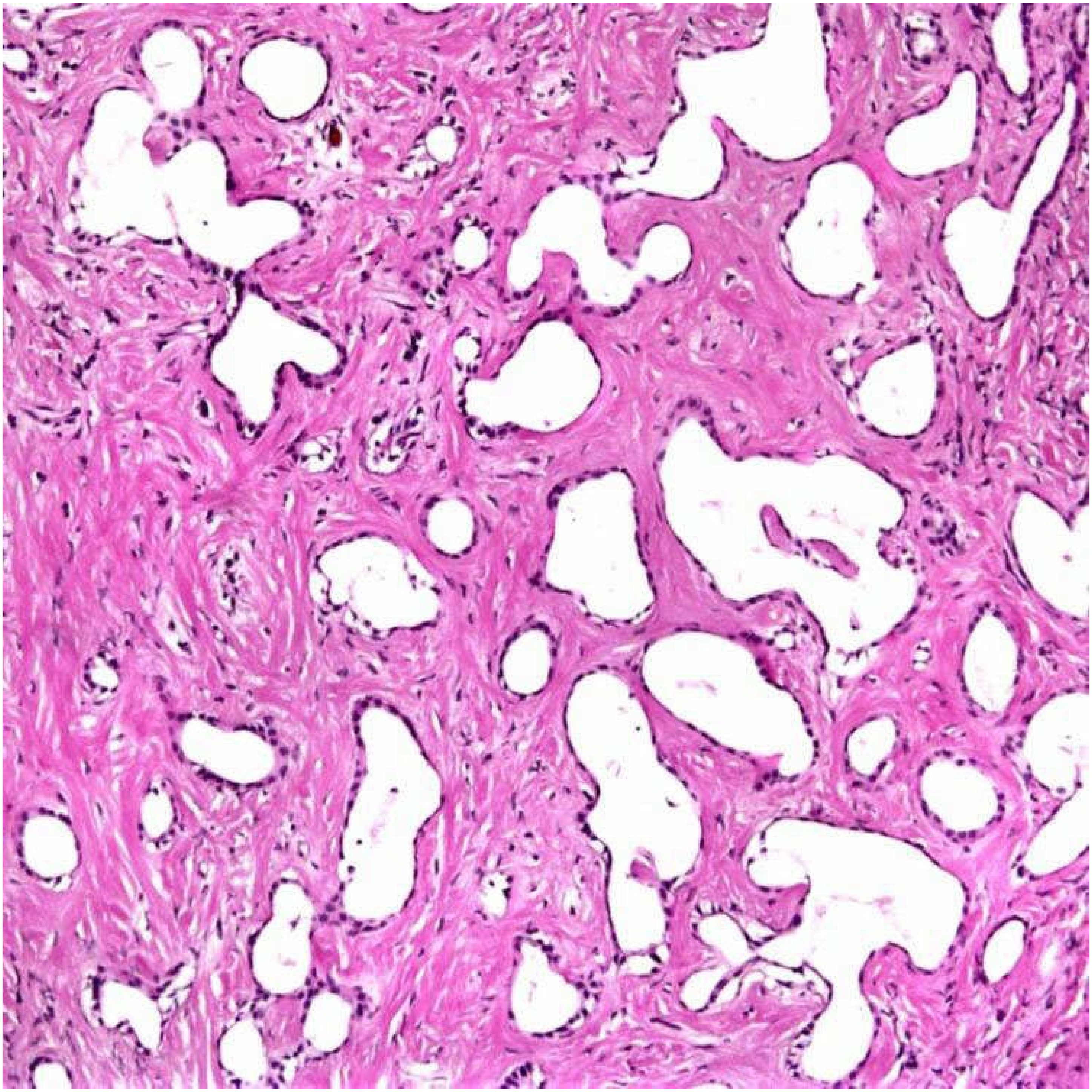
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Multiple widely scattered VMC raise possibility of associated congenital hepatic fibrosis or polycystic liver disease



VMCs are typically located within or at the edge of portal tracts.



The typical appearance of VMC is that of angulated, somewhat dilated glands lined by biliary epithelium that are present within dense, fibrous stroma.

SELECTED REFERENCES

1. Hornick, JL, et al. Immunohistochemistry can help distinguish metastatic pancreatic adenocarcinomas from bile duct adenomas and hamartomas of the liver. *Am J Surg Pathol*. 2005; 29(3):381–389.
2. Varnholt, H, et al. Biliary adenofibroma: a rare neoplasm of bile duct origin with an indolent behavior. *Am J Surg Pathol*. 2003; 27(5):693–698.
3. Jain, D, et al. Evidence for the neoplastic transformation of Von-Meyenburg complexes. *Am J Surg Pathol*. 2000; 24(8):1131–1139.
4. Desmet, VJ. Congenital diseases of intrahepatic bile ducts: variations on the theme “ductal plate

malformation”. *Hepatology*. 1992; 16(4):1069–1083.
5.Karhunen, PJ. Adult polycystic liver disease and biliary microhamartomas (von Meyenburg’s complexes). *Acta Pathol Microbiol Immunol Scand A*. 1986; 94(6):397–400.

Mucinous Cystic Neoplasm

KEY FACTS

Clinical Issues

- Almost exclusively occurs in women
- CA19-9 and CEA in cyst fluid helps differentiate between simple cyst and mucinous cystic neoplasm (MCN)

Macroscopic

- Solitary, multiloculated cystic neoplasm
- Clear, mucinous, or opalescent cystic fluid
- Cyst lining may be smooth, trabeculated, or have papillary excrescences
- Thickened, nodular areas suggest malignancy
- Several cm to > 20 cm

Microscopic

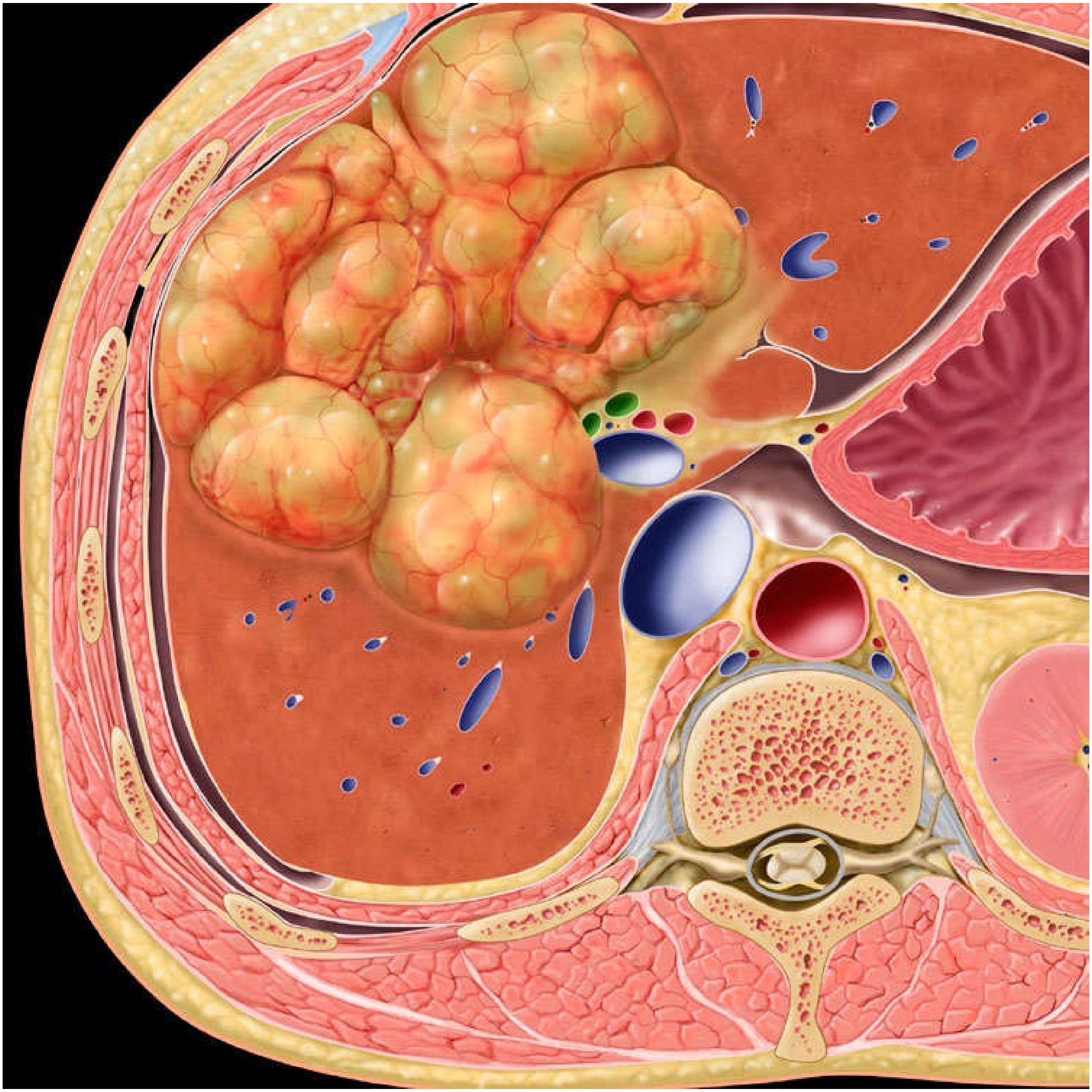
- Similar to mucinous cystic neoplasm of pancreas
  - MCN
  - Lined by mucinous columnar epithelium with focal cuboidal, flattened, or papillary areas
  - May have gastric or intestinal metaplasia
  - Varying degrees of dysplasia may be present
  - Densely cellular ovarian-like stroma positive for ER, PR, and inhibin
- MCN with associated invasive carcinoma
  - Most arise from preexisting MCN
  - Invasion of underlying stroma by malignant glands or single cells

Top Differential Diagnoses

- Cystic variant of biliary intraductal papillary neoplasm
- Solitary bile duct cysts
- Ciliated hepatic foregut cyst
- Endometrial cyst

Diagnostic Checklist

- Multilocular cystic neoplasm lined by mucinous epithelial cells with underlying ovarian-type stroma



Schematic Representation
Graphic shows a lobulated, complex cystic mass with a vascularized wall, areas of solid growth, and well-defined septa typical of mucinous cystic neoplasm (MCN) of the liver.

TERMINOLOGY

Abbreviations

- Mucinous cystic neoplasm (MCN)

Definitions

- Cystic biliary neoplasm arising within liver or in extrahepatic biliary tree, including gallbladder
- Formerly known as biliary cystadenoma and cystadenocarcinoma

ETIOLOGY/PATHOGENESIS

Unknown

- May originate from müllerian remnants misplaced during embryogenesis
- Proliferation of endodermally derived epithelium and primitive mesenchyme stimulated by female sex hormone

CLINICAL ISSUES

Epidemiology

- Incidence
  - Rare; < 5% of cystic lesions of liver
- Age
  - Average: 40-50 years
- Sex
  - Almost exclusively occurs in women

Presentation

- Pain, mass, and occasionally jaundice
  - Some patients are asymptomatic

Laboratory Tests

- CA19-9 and CEA in cyst fluid helps differentiate between simple cyst and MCN

Treatment

- Surgical approaches
  - Complete resection

Prognosis

- Complete surgical resection should be curative
  - Incompletely resected tumor may recur or undergo malignant transformation

IMAGING

Ultrasonographic Findings

- Large, well-defined, multiloculated, anechoic mass with highly echogenic septations
- Mural or septal calcifications or fluid levels

CT Findings

- Nonenhanced CT
  - Large, well-defined, homogeneous, hypodense heterogeneous mass (cystic and hemorrhagic areas)
  - NCN: Septations without nodularity
  - MCN with associated invasive carcinoma: Septations and nodularity
  - Fine mural or septal calcifications
  - Biliary dilatation
- Contrast-enhanced CT
  - Nonenhancing cystic spaces
  - Enhancement of internal septa, capsule, and papillary excrescences or nodules
  - Fine mural or septal calcifications

MACROSCOPIC

General Features

- Solitary, multiloculated cystic neoplasm
  - Typically large with variable amount of internal septations
  - Clear, straw-colored, mucinous, or opalescent cystic fluid
    - Rarely hemorrhagic or purulent
  - Cyst lining may be smooth, trabeculated, or have papillary excrescences
    - Thickened areas suggest malignancy, and extensive sampling is warranted

Size

- Several cm to > 20 cm

MICROSCOPIC

Histologic Features

- MCN
  - Cystic spaces are lined by columnar epithelium
    - Focally may be cuboidal, flattened, or papillary
    - Epithelium almost always contain mucin that stains positive with Alcian blue or mucicarmine
    - Gastric-type or intestinal metaplasia may be present
    - Epithelial cells immunoreactive to CK8, CK18, CK7, and CK19

- ○ Densely cellular ovarian-type stroma
  - – Only present in women
  - – Immunoreactive to estrogen and progesterone receptors and inhibin
- ○ Varying degrees of dysplasia may be present: Low-grade dysplasia and high-grade dysplasia (carcinoma in situ)

- MCN with associated invasive carcinoma
  - ○ Cytological atypia and mitoses in epithelial lining cells
  - ○ Invasion of underlying stroma by malignant glands or single cells
  - ○ Ovarian-type stroma present in female patients

DIFFERENTIAL DIAGNOSIS

Cystic Variant of Intraductal Papillary Neoplasm of Bile Ducts

- No gender predilection and lack of ovarian-type stroma
- Prominent papillary proliferation with fibrovascular cores
- Communication with prominent, cystically dilated bile duct

Solitary Biliary Cyst

- Asymptomatic, often incidental findings
- Usually unilocular
- No gender predilection
- Lack of ovarian-type stroma

Ciliated Hepatic Foregut Cyst

- Ciliated epithelium
- Usually small, asymptomatic, incidental findings
- No gender predilection
- Lack of ovarian-type stroma

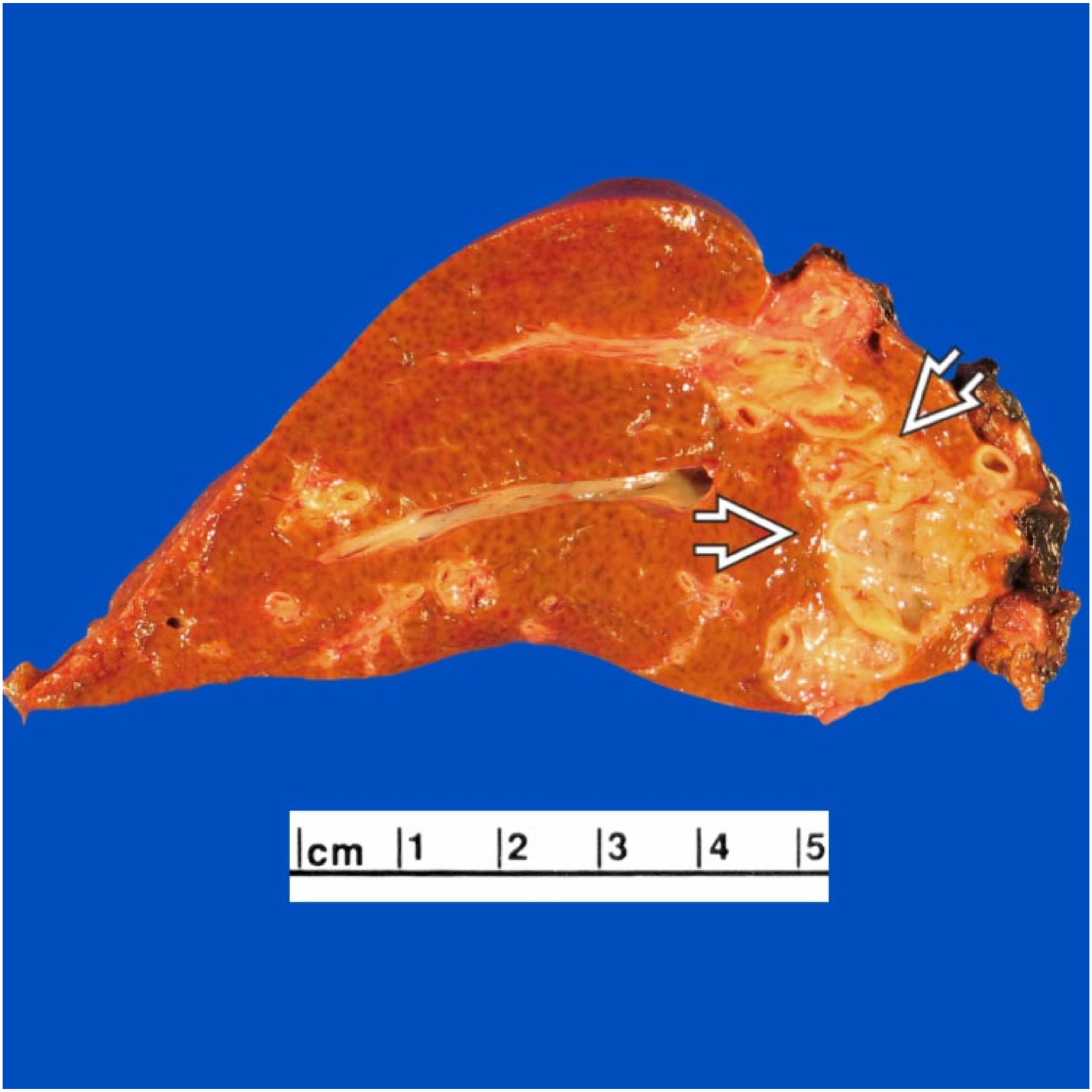
Endometrial Cyst

- Positive ER and PR and negative α-inhibin stainings within both epithelium and stroma
- ER, PR, and α-inhibin only positive in stromal cells in MCN and MCN with associated invasive carcinoma, but not in cystic lining epithelium
- CD10(+) in stromal cells in endometrial cyst but not in MCN

DIAGNOSTIC CHECKLIST

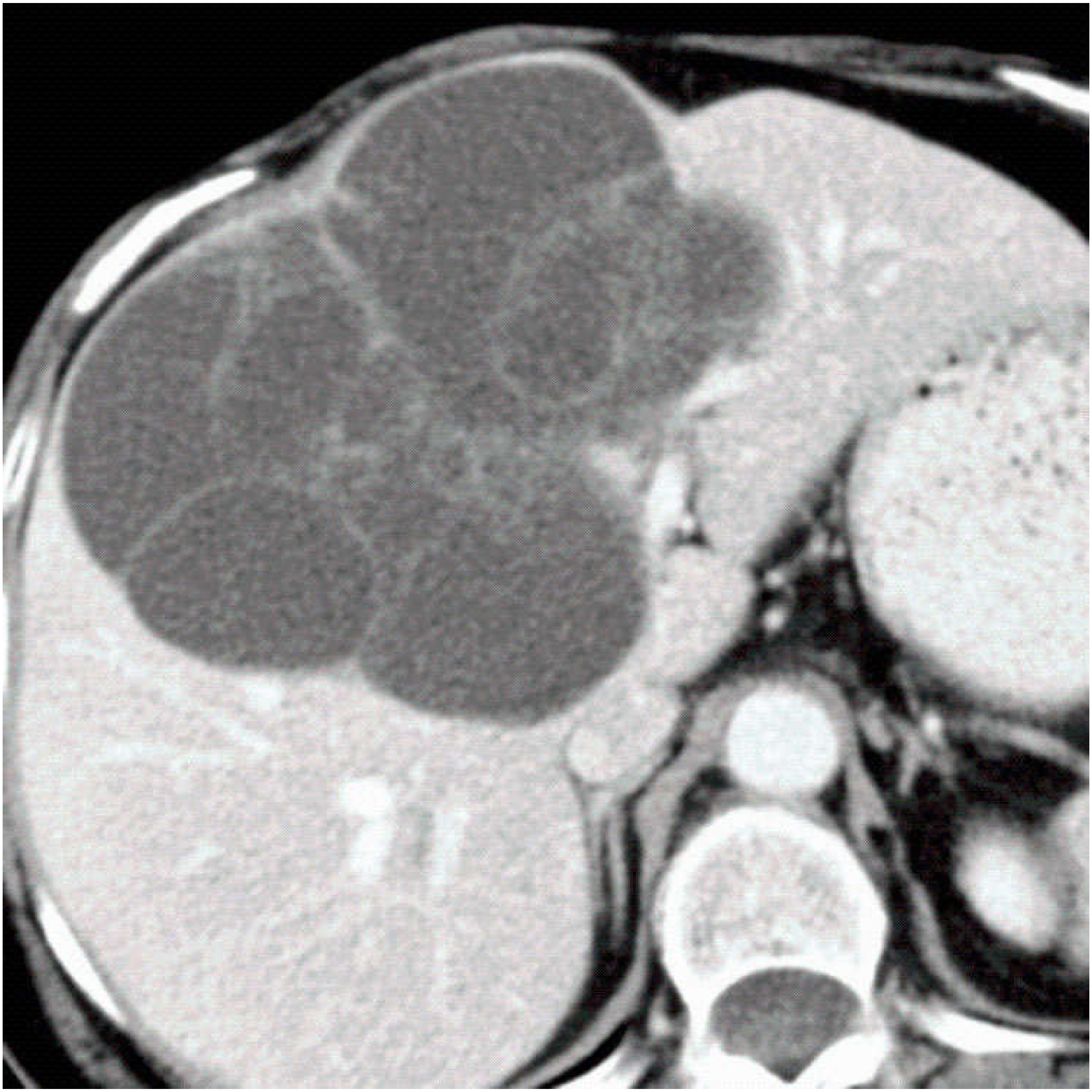
Pathologic Interpretation Pearls

• Multilocular cystic neoplasm lined by mucinous epithelial cells with underlying ovarian-type stroma

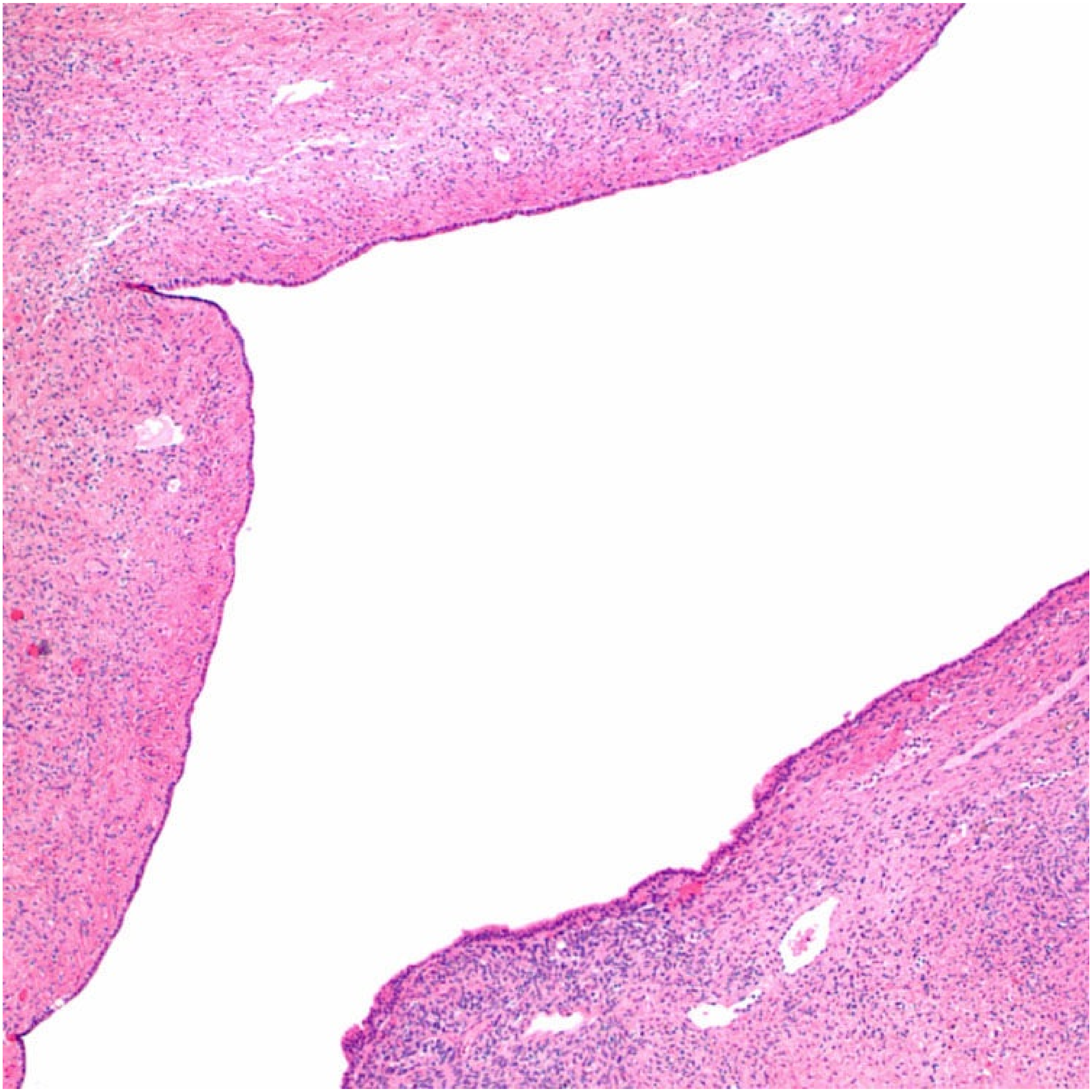


Gross Specimen

This MCN consists of a multiloculated, cystic tumor that is visible on the cut surface of the specimen .

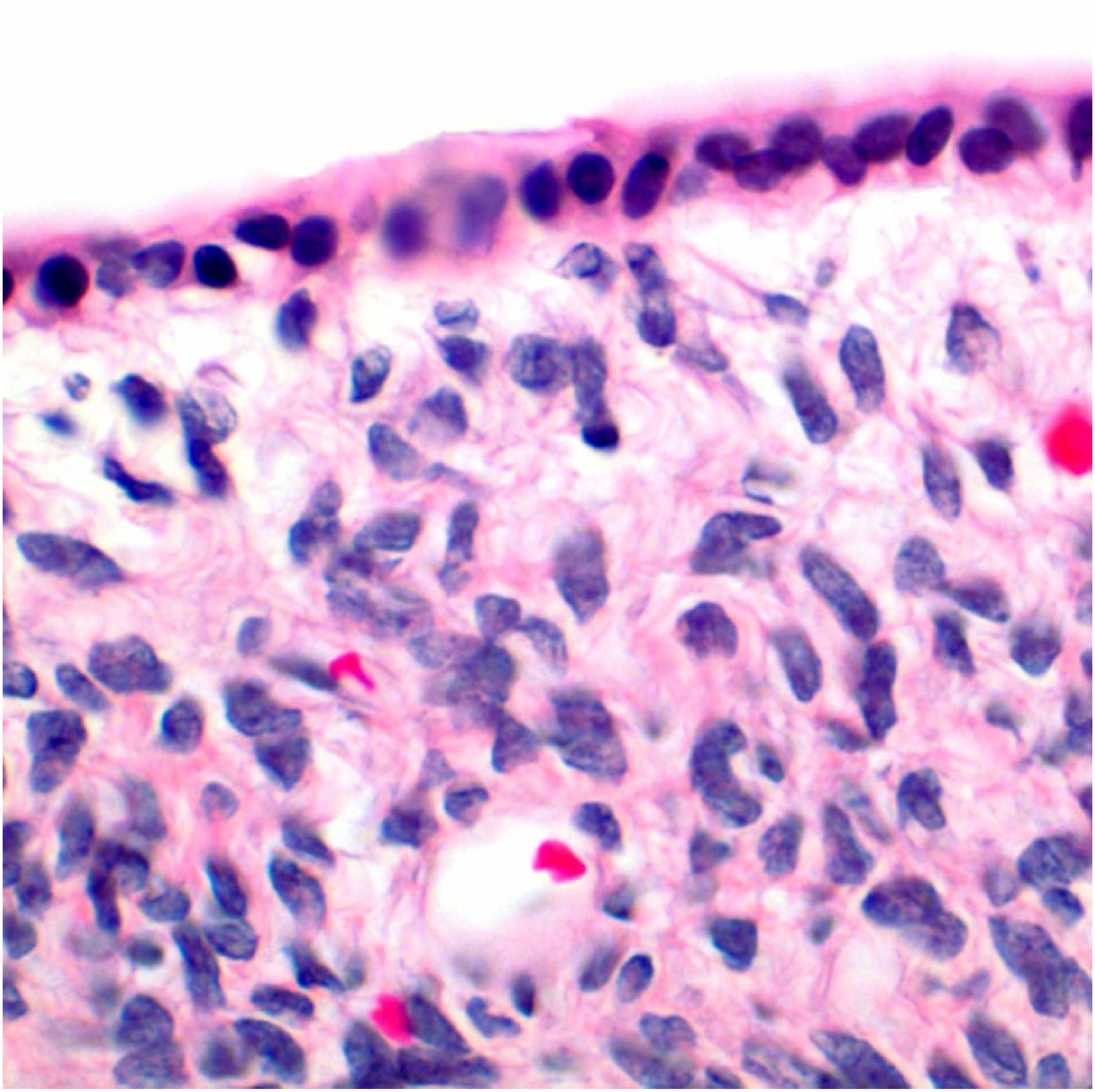


Complex Multiloculated Cystic Mass
Axial CECT shows a complex MCN in the liver with lobulated margins and an enhancing wall and septa, typical findings.

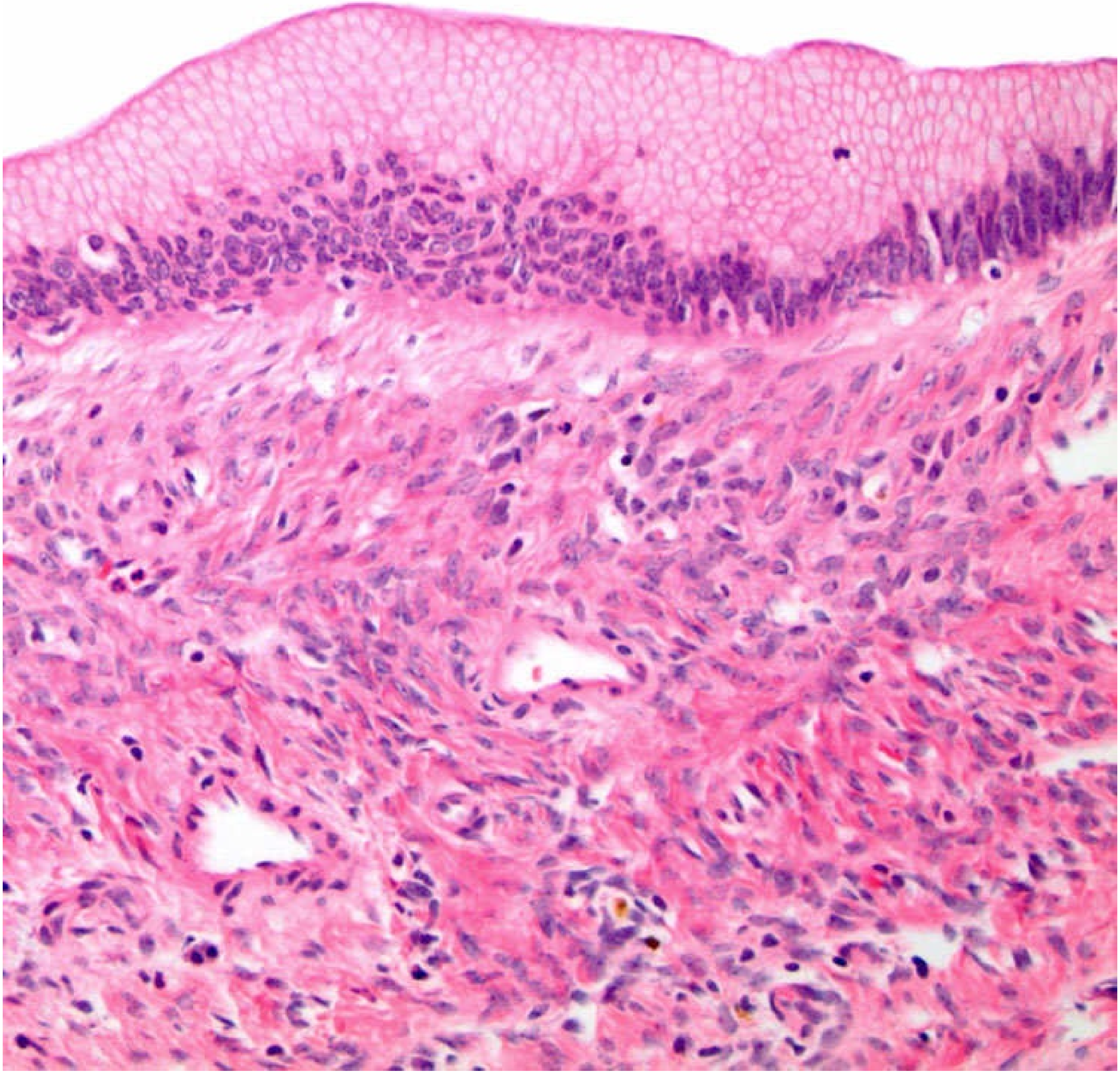


Ovarian-Type Stroma

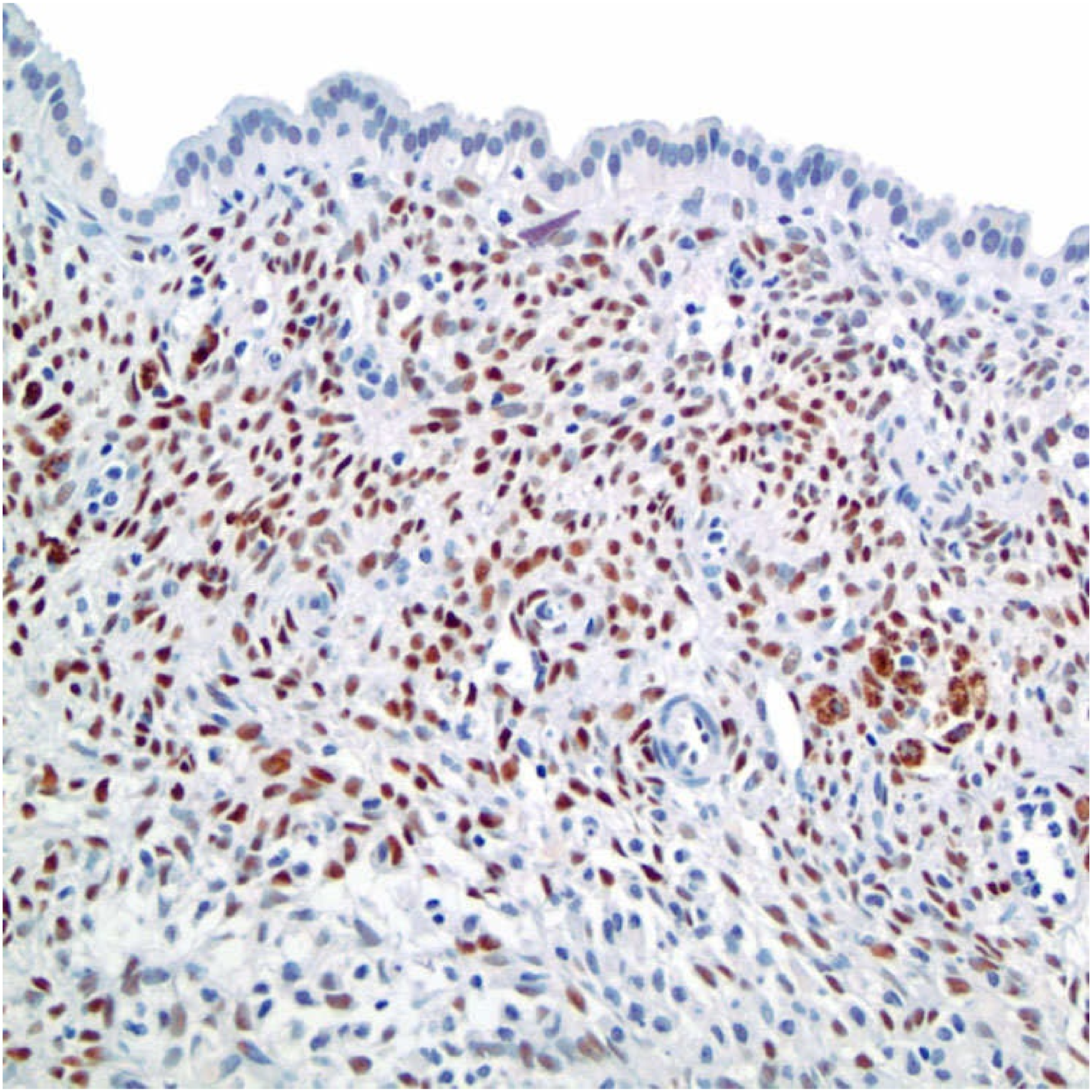
MCN of the liver is composed of cystic spaces lined by cuboidal or low columnar biliary epithelium. The ovarian-type stroma, composed of abundant spindly cells, is visible even at low power.



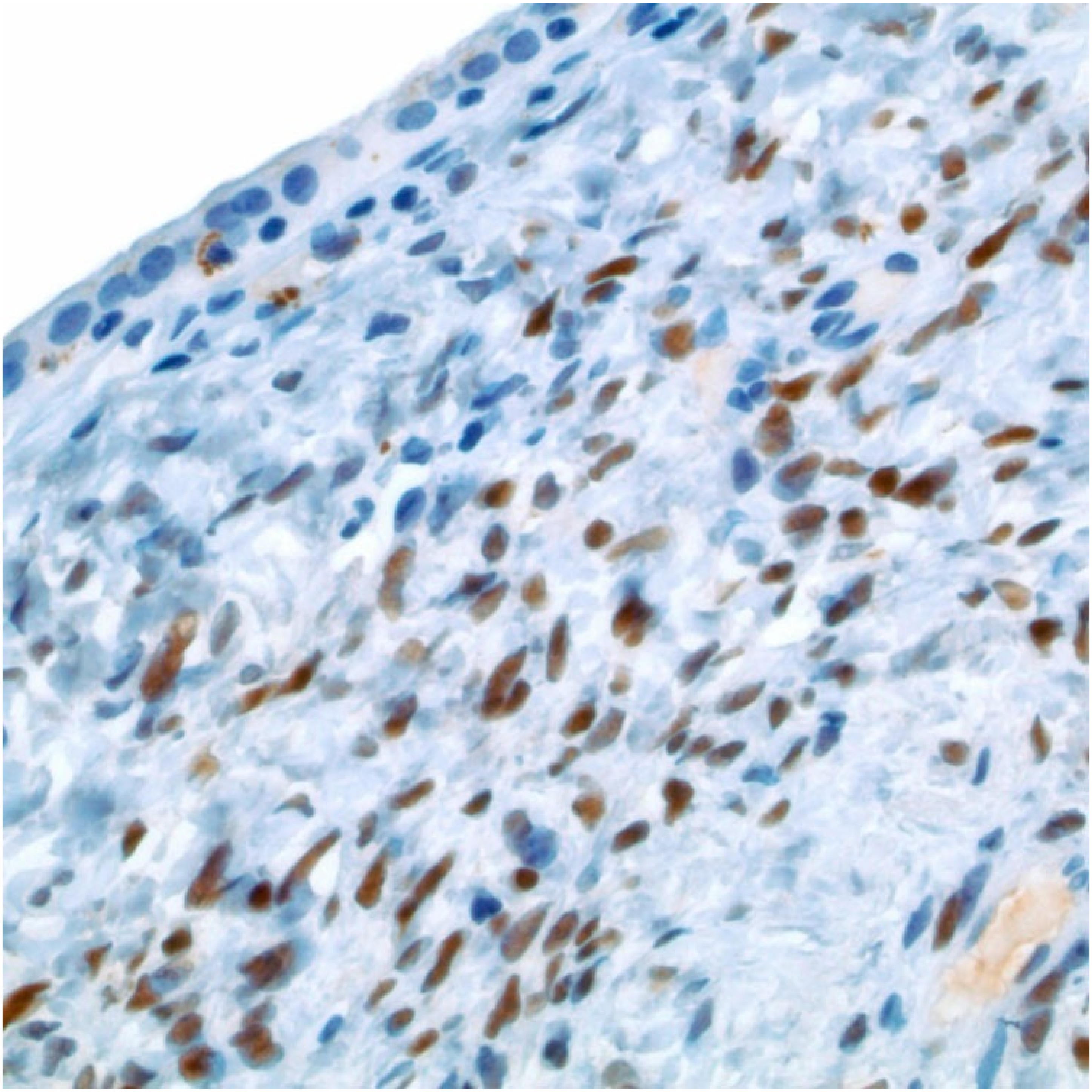
Lining Epithelial Cells
The lining epithelial cells of MCN of the liver are typically simple columnar cells without cytologic atypia.
Note the underlying cellular stroma composed of spindly cells.



Gastric-Type Metaplasia
The lining epithelial cells in MCN may show gastric-type metaplasia with cytoplasmic mucin.

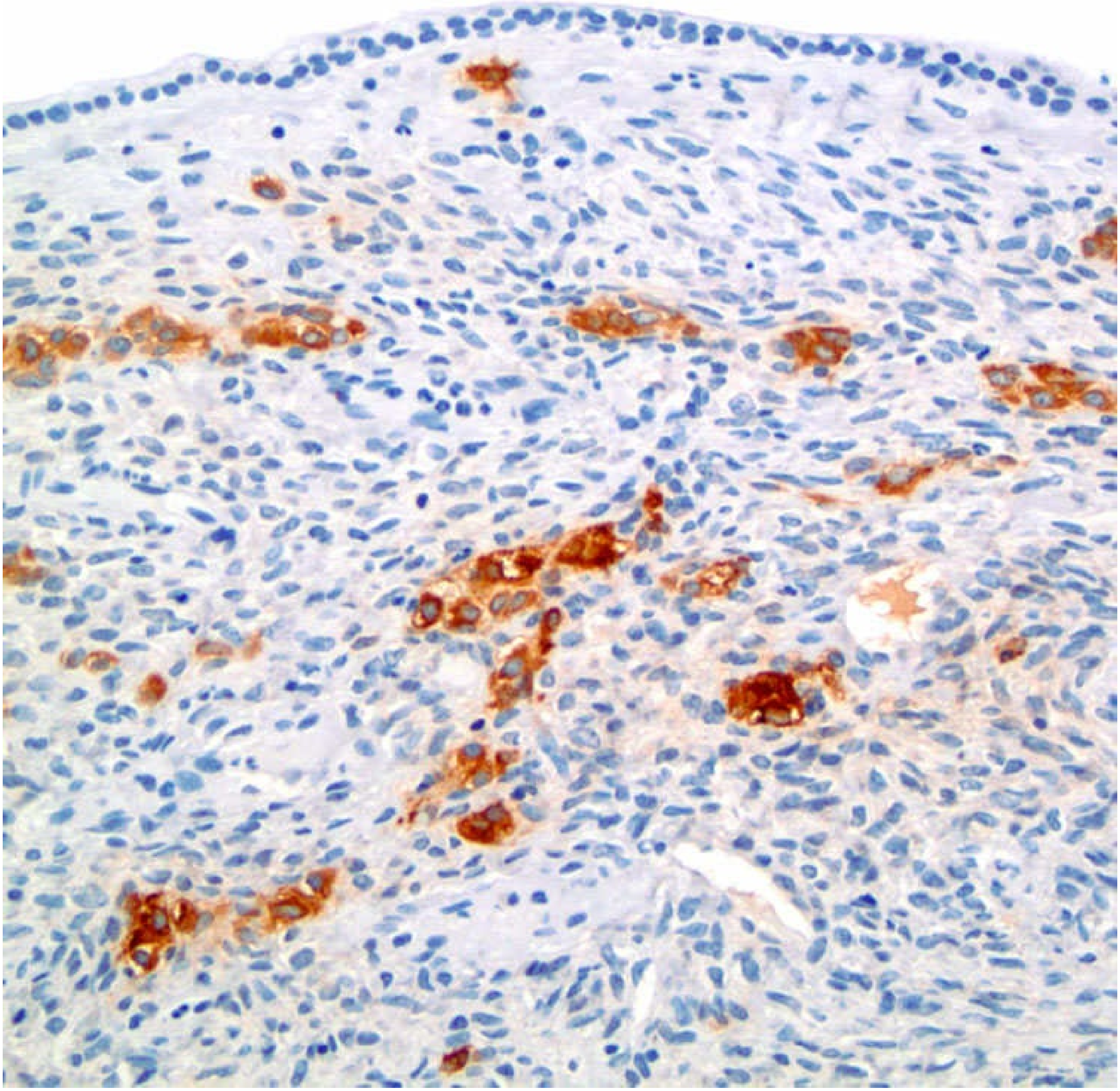


PR Stain
The stromal cells in MCN are positive for progesterone receptor (PR) upon immunohistochemical staining.

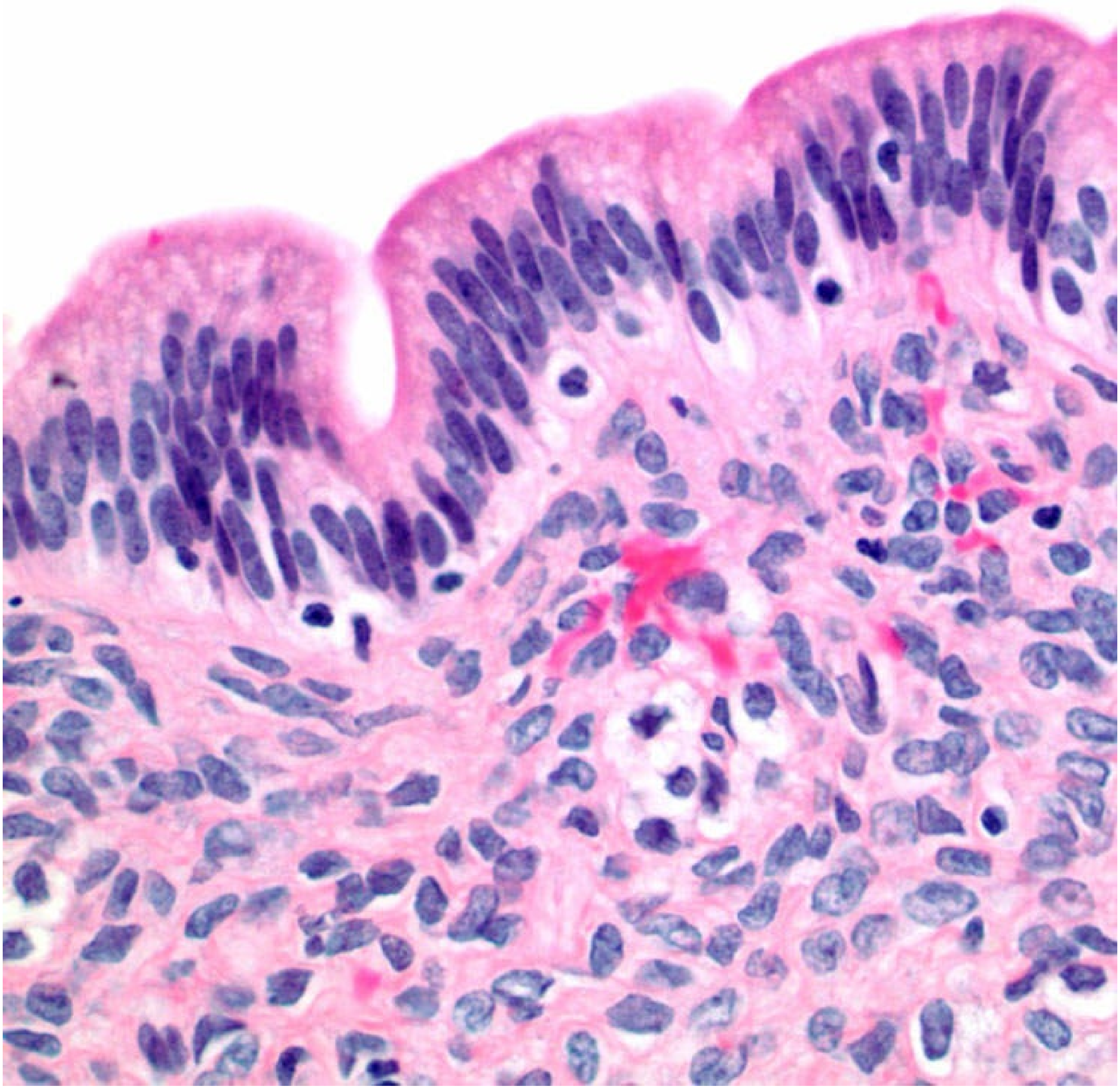


ER Stain

The stromal cells in MCN are positive for estrogen receptor (ER) upon immunohistochemical staining.

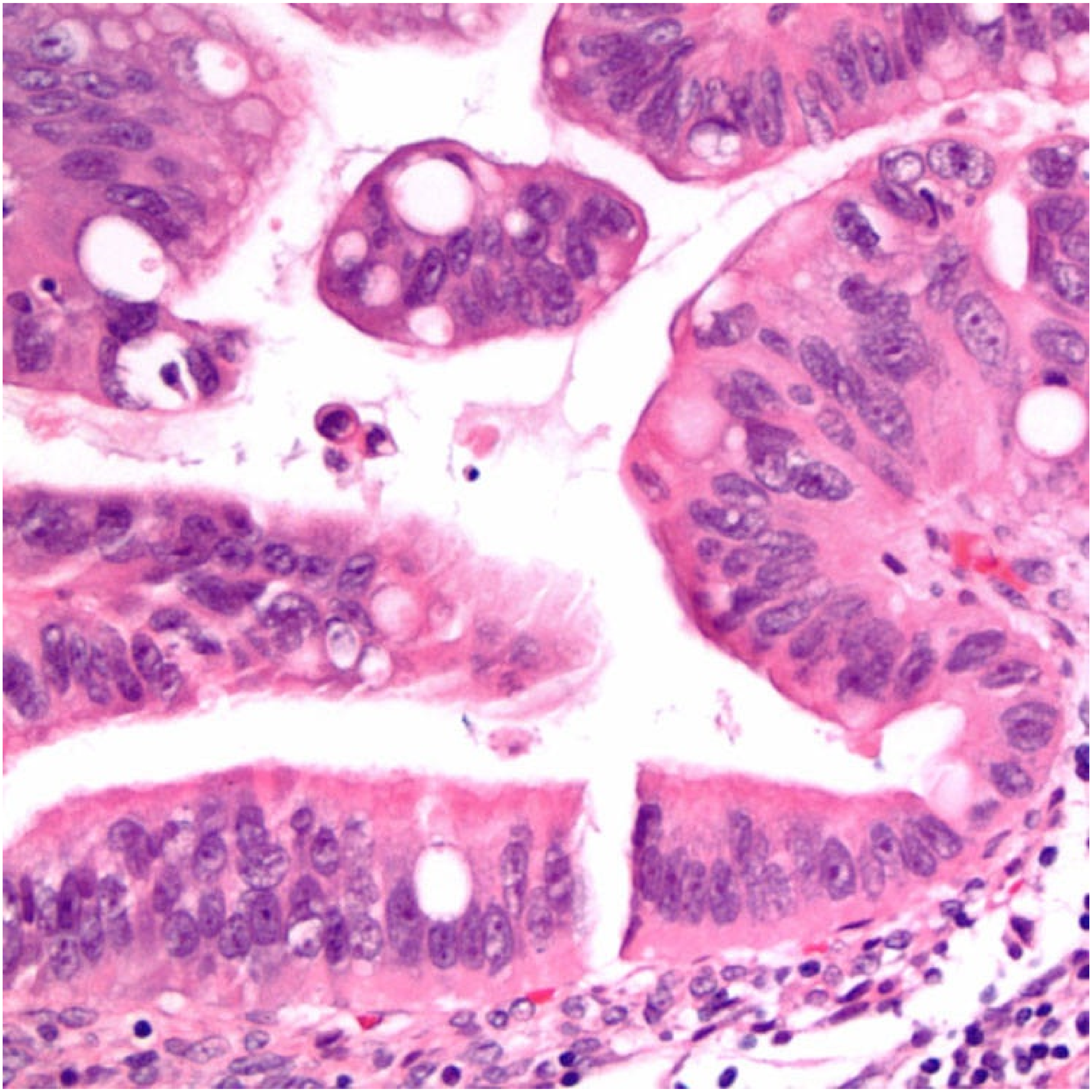


Inhibin Stain
The stromal cells in MCN can be focally positive for inhibin on immunohistochemical staining.

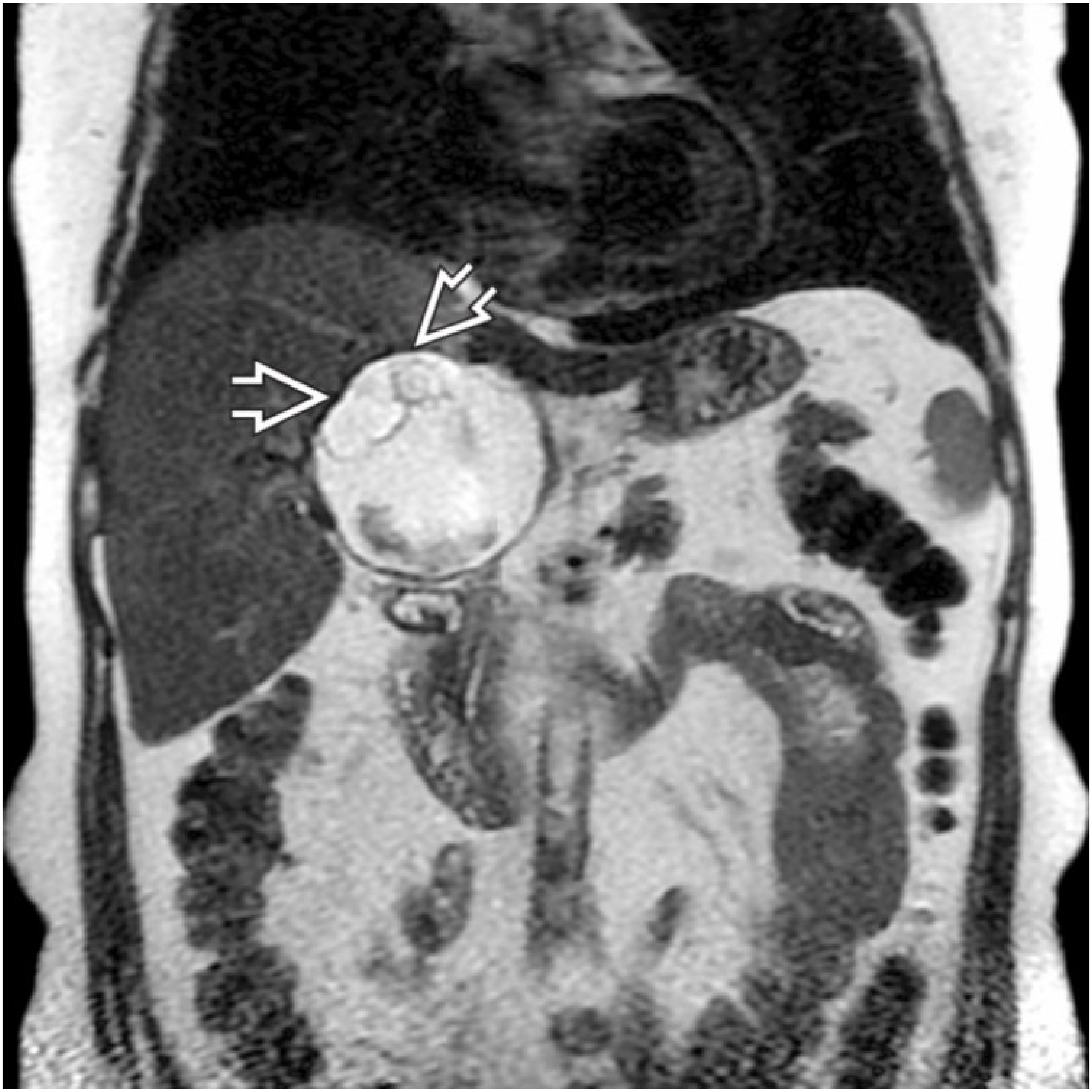


Low-Grade Dysplasia

This MCN shows low-grade dysplasia with enlarged, hyperchromatic, and crowded nuclei in the biliary-type epithelial cells lining the cysts. The dysplastic nuclei still maintain the polarity with the axis perpendicular to the basement membrane.

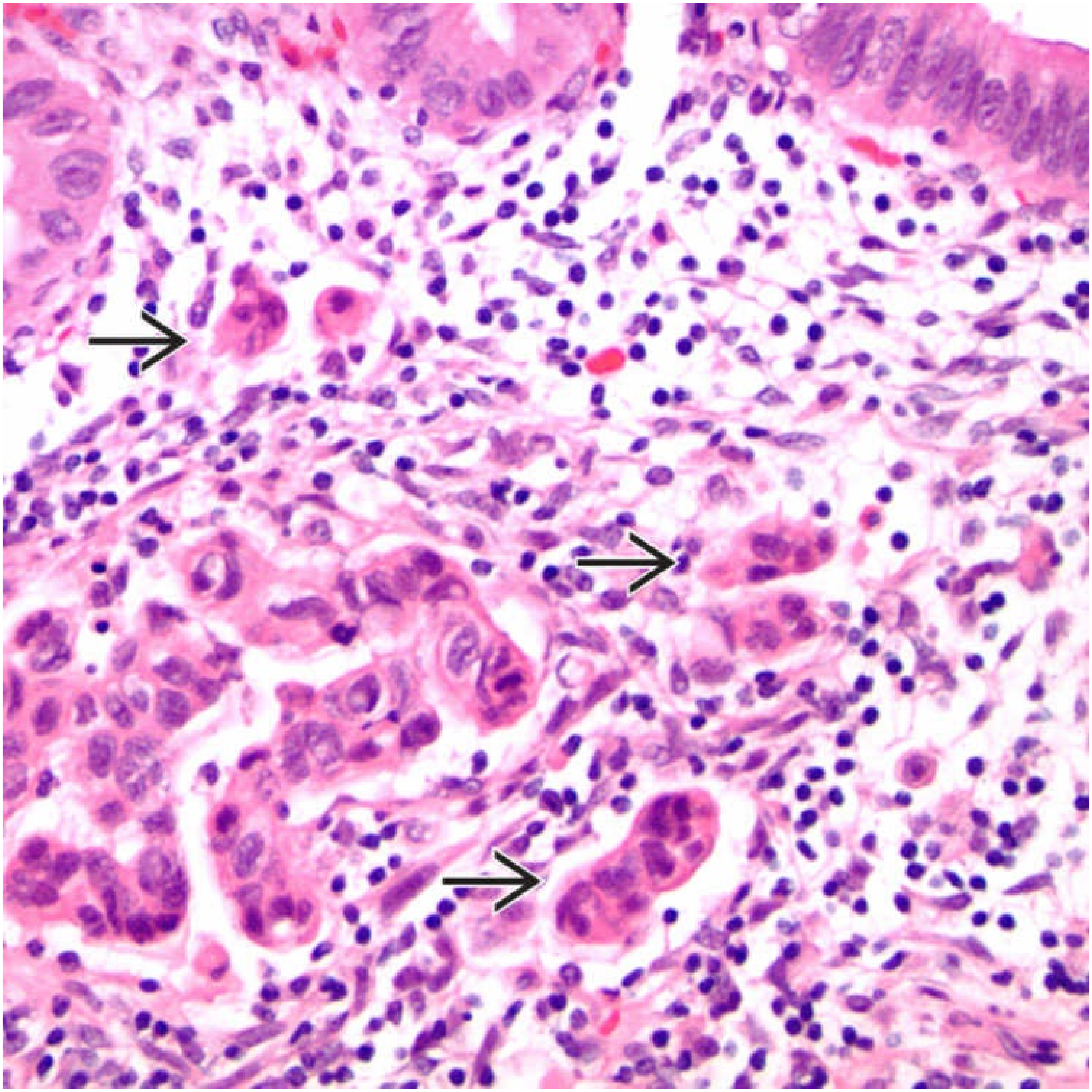


High-Grade Dysplasia
This MCN shows high-grade dysplasia in the lining epithelial cells, which are characterized by crowded and hyperchromatic nuclei with loss of polarity.



Complex Cystic Mass

MR of MCN shows a complex cystic mass in the liver with areas of nodular wall thickening ⇨. (Courtesy R. Bentley, MD.)



Focal Invasion
This adenocarcinoma arising in a MCN shows focal invasion of the underlying stroma →.

SELECTED REFERENCES

1.Basturk, O, et al. A Revised Classification System and Recommendations From the Baltimore Consensus Meeting for Neoplastic Precursor Lesions in the Pancreas. *Am J Surg Pathol*. 2015; 39(12):1730–1741.

2.Zen, Y, et al. Intraductal papillary neoplasms and mucinous cystic neoplasms of the hepatobiliary

system: demographic differences between Asian and Western populations, and comparison with pancreatic counterparts. *Histopathology*. 2014; 65(2):164–173.
3. Zen, Y, et al. Mucinous cystic neoplasms of the liver: a clinicopathological study and comparison with intraductal papillary neoplasms of the bile duct. *Mod Pathol*. 2011; 24(8):1079–1089.
4. Lam, MM, et al. Ovarian-type stroma in hepatobiliary cystadenomas and pancreatic mucinous cystic neoplasms: an immunohistochemical study. *Am J Clin Pathol*. 2008; 129(2):211–218.
5. Zen, Y, et al. Biliary cystic tumors with bile duct communication: a cystic variant of intraductal papillary neoplasm of the bile duct. *Mod Pathol*. 2006; 19(9):1243–1254.
6. Weihing, RR, et al. Hepatobiliary and pancreatic mucinous cystadenocarcinomas with mesenchymal stroma: analysis of estrogen receptors/progesterone receptors and expression of tumor-associated antigens. *Mod Pathol*. 1997; 10(4):372–379.
7. Devaney, K, et al. Hepatobiliary cystadenoma and cystadenocarcinoma. A light microscopic and immunohistochemical study of 70 patients. *Am J Surg Pathol*. 1994; 18(11):1078–1091.
8. Wheeler, DA, et al. Cystadenoma with mesenchymal stroma (CMS) in the liver and bile ducts. A clinicopathologic study of 17 cases, 4 with malignant change. *Cancer*. 1985; 56(6):1434–1445.

Intrahepatic Cholangiocarcinoma

KEY FACTS

Terminology

- Primary adenocarcinoma arising from biliary epithelium in liver

Clinical Issues

- Incidence
  - 2nd most common primary liver cancer after hepatocellular carcinoma
  - Has been increasing around world, including USA
  - Very prevalent in Asia, particularly in northeastern Thailand
  - Equal frequency in men and women
- Well-known risk factors include liver fluke infection, primary sclerosing cholangitis, hepatolithiasis, Thorotrast exposure, congenital anomalies of bile ducts
- Serum level of CA19-9 is commonly elevated
- Most patients are diagnosed with advanced stages of disease
  - Dismal prognosis

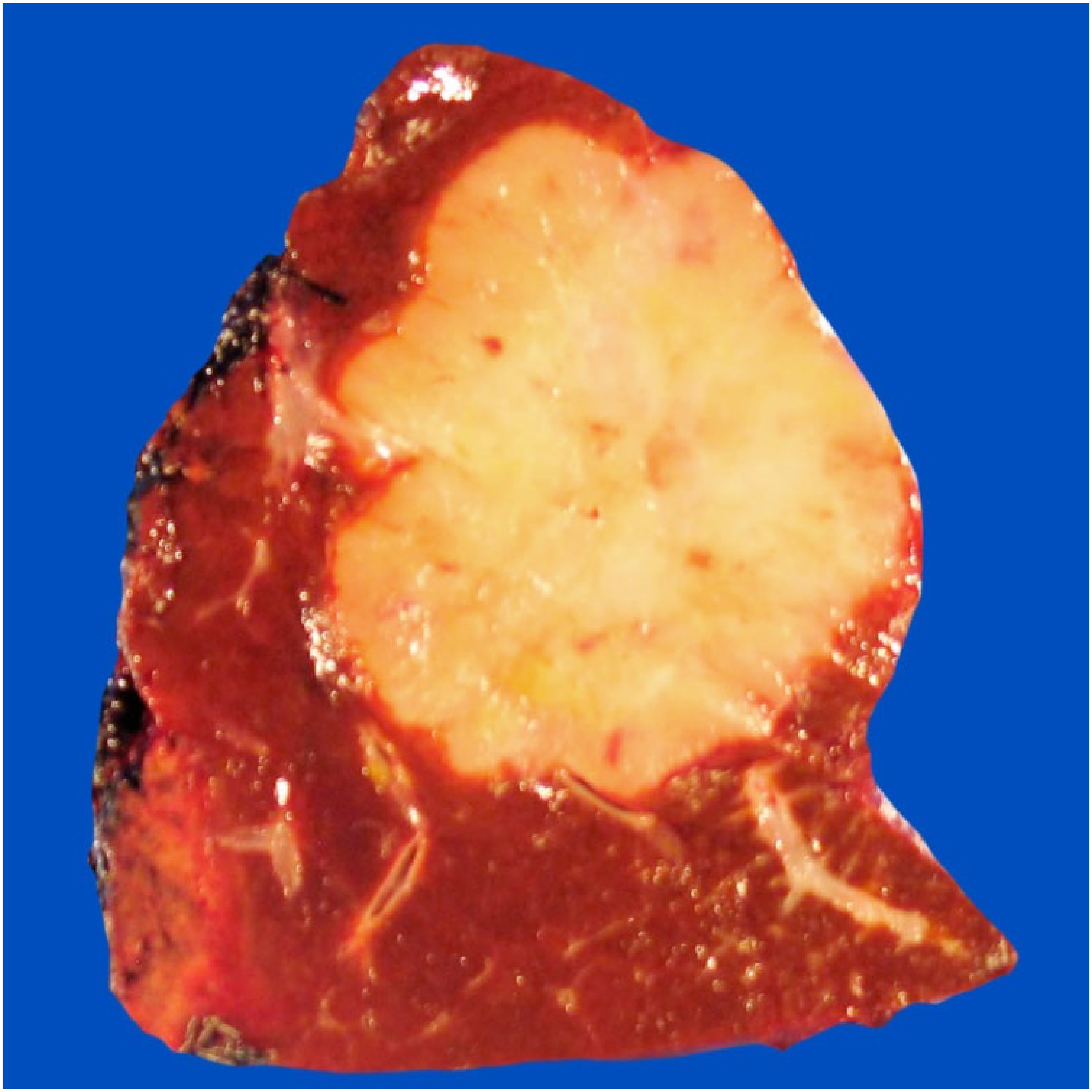
Microscopic

- Well- to moderately differentiated adenocarcinoma
  - Desmoplastic stroma
  - Frequently shows perineural invasion
  - Mucin typically present
  - CK19, CK7 positive
- Neoplastic cells can form glands, solid nests, cords, or papillary structures

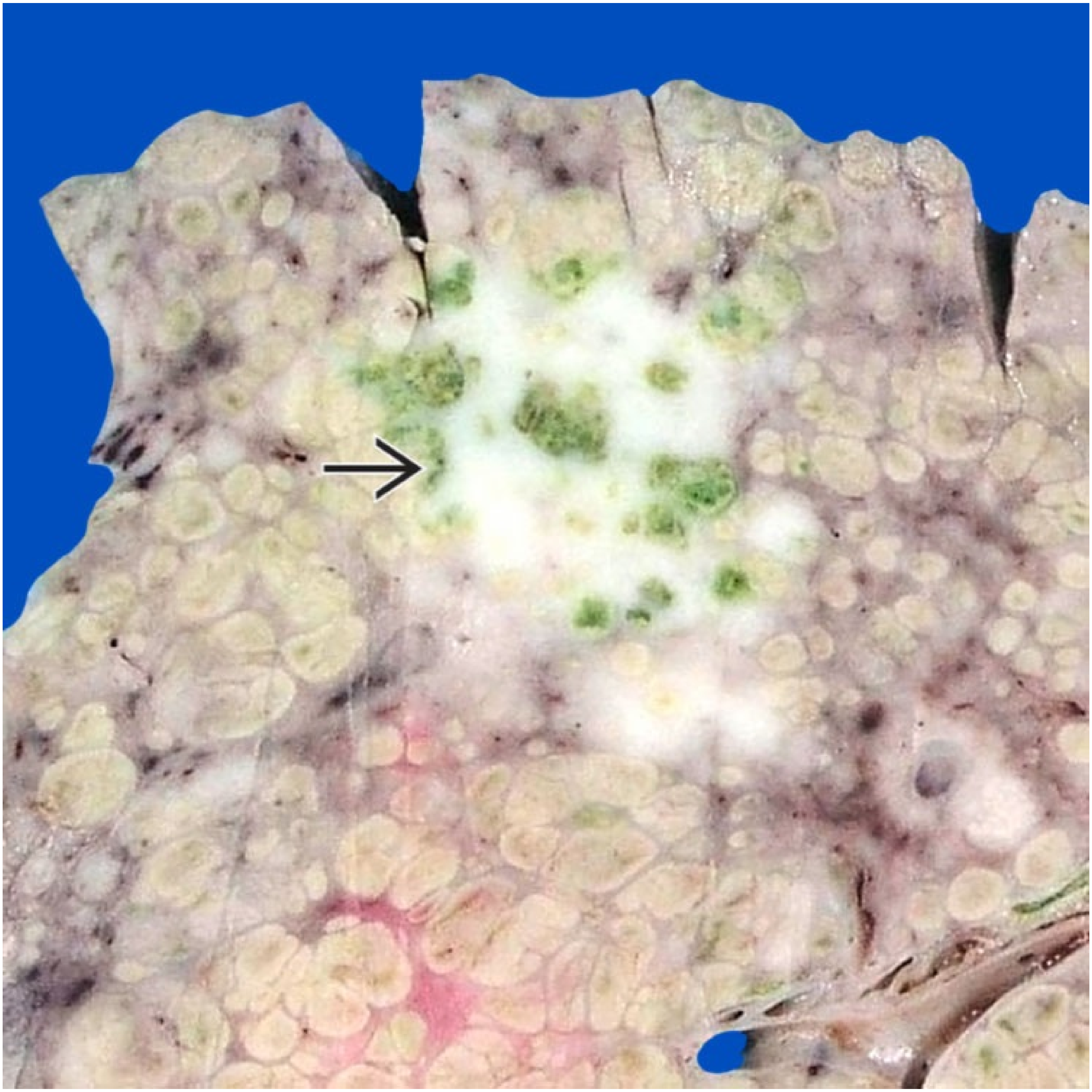
Top Differential Diagnoses

- Hepatocellular carcinoma
- Metastatic adenocarcinoma
- Epithelioid hemangioendothelioma
- Bile ductular reaction or atypical biliary epithelium due to inflammation

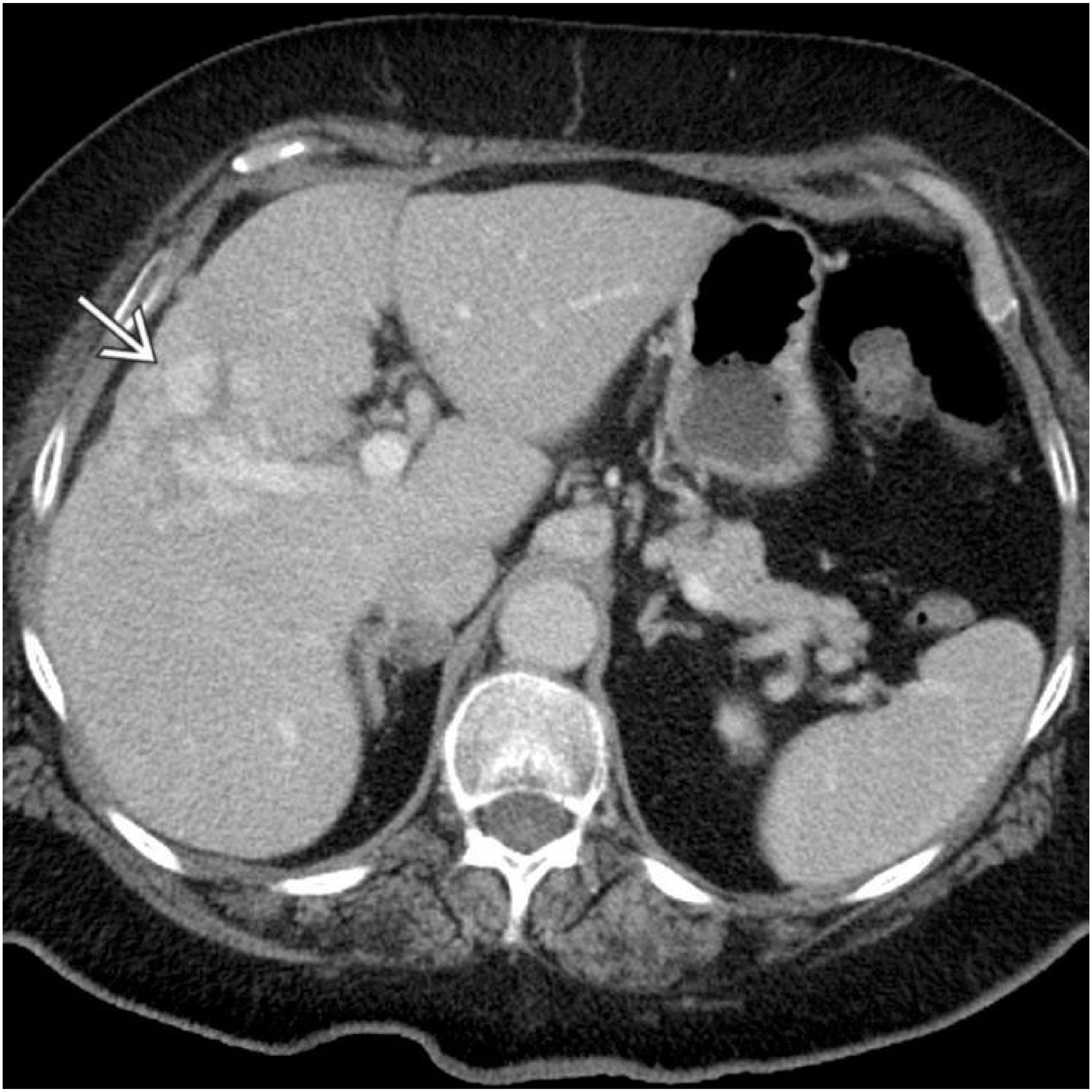
• Benign hamartoma
• Biliary adenofibroma
• Hyperplasia of peribiliary glands



Intrahepatic Cholangiocarcinoma Arising in Noncirrhotic Liver
Gross photograph shows a white-tan, firm, and distinct mass in a noncirrhotic liver.

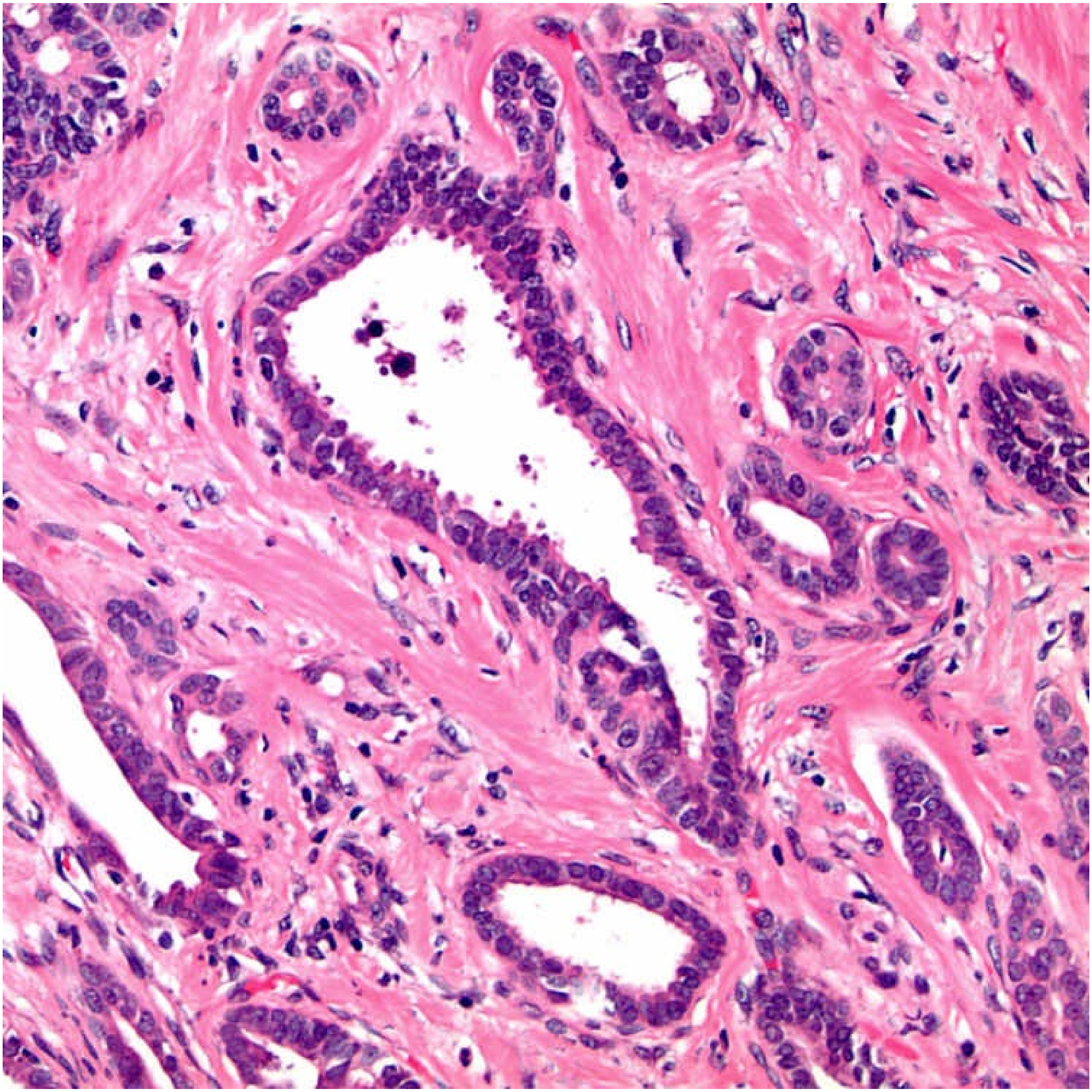


Intrahepatic Cholangiocarcinoma in Cirrhosis
A white, green to tan, irregular, firm mass → is shown in this case of hepatitis C-associated cirrhosis.
There is increased risk for cholangiocarcinoma in cirrhosis.



CECT of Intrahepatic Cholangiocarcinoma

Axial reformatted CECT in portal venous phase shows a heterogeneous hepatic mass ⇨ within a noncirrhotic liver. Satellite lesions of similar appearance are present as well.



Well-Differentiated Appearance
H&E shows infiltrative, well-formed glands with minimal nuclear atypia in a prominent fibrous stroma.

TERMINOLOGY

Definitions

• Primary adenocarcinoma arising from biliary epithelium

ETIOLOGY/PATHOGENESIS

Multistep Carcinogenesis

- Chronic inflammation may be common pathogenic pathway
  - Wide array of genetic changes have been described, including *TP53* and *KRAS* mutations
  - Mutations in isocitrate dehydrogenase (IDH) 1 and 2
    - Observed in 25-30% of cases
    - Uncommon in extrahepatic cases and adenocarcinomas of other gastrointestinal sites

CLINICAL ISSUES

Epidemiology

- Incidence
  - 2nd most common primary liver cancer after hepatocellular carcinoma
  - Varies widely worldwide; more prevalent in East Asia than in Western countries
- Age
  - Average at presentation: 60 years
- Sex
  - Equal frequency in men and women
- Ethnicity
  - Very prevalent in Asia, particularly in Northeastern Thailand (associated with liver fluke infestation), East Asia

Presentation

- 10-20% of primary liver malignancies
  - Incidence and mortality rates have been increasing in several regions around world
  - Incidence has also increased 3x in past few decades in USA
- Most patients diagnosed with advanced stages of disease
- Symptoms: Abdominal pain, weight loss, malaise, jaundice

Laboratory Tests

- CA19-9 serum level currently most important tumor marker
- Alkaline phosphatase and bilirubin variably elevated

Treatment

- Surgical resection
  - Gemcitabine-based therapy
    - For unresectable cases or for tumors with positive resection margin

Prognosis

- Long-term survival is dismal

Risk Factors

- Liver fluke infection
  - *Clonorchis sinensis*
  - *Opisthorchis viverrini*
- Primary sclerosing cholangitis
- Hepatolithiasis
- Thorotrast exposure
  - Radiographic contrast medium widely used from 1930-1955
- Congenital anomalies of bile ducts
  - Choledochal cysts
  - Polycystic liver disease
  - Caroli's disease
  - Congenital hepatic fibrosis
- Hepatitis B and C
- Alcohol use, cirrhosis
- Exposure to organic solvents has been reported
  - Recent outbreak among printing company workers in Japan

IMAGING

General Features

- Single well-defined, predominantly homogeneous mass with irregular borders
- Satellite or daughter nodules frequent and vary in size

MR Findings

- Rim-like enhancement may be seen around periphery of tumor on arterial phase and as gradual centripetal enhancement on delayed phase
- Entire mass may be enhanced only on delayed phase images
- Capsular retraction is common
- Dilatation of bile ducts peripheral to tumor is common

CT Findings

- Similar to MR findings

MACROSCOPIC

General Features

- Firm, irregular, white-tan fibrotic single or multiple masses with infiltrative borders
  - Most commonly arising in noncirrhotic liver
  - Can be classified into 3 subtypes based on gross morphological features
  - Mass forming
    - Most common type

– Definite mass forms within liver parenchyma

○ Periductal infiltrating

– Tumor grows longitudinally along large bile ducts

○ Intraductal

– Tumor grows toward lumina of large bile ducts with papillary pattern

MICROSCOPIC

Histologic Features

- Usually well- to moderately differentiated adenocarcinoma
  - ○ Neoplastic cells can form glands, solid nests, cords, or papillary structures
  - ○ Tumor cells columnar to cuboidal with eosinophilic and granular cytoplasm
- Desmoplastic stroma surrounding carcinoma cells
- Mucin is typically present
  - ○ Either intracytoplasmic or extracellular
    - – May be demonstrated by mucicarmine, PAS-D, or Alcian blue
- Immunopositive for CK7, CK19, MOC-31, CDX-2 (variable), villin (variable brush border pattern)
- Uncommon variants include
  - ○ Adenosquamous
  - ○ Squamous
  - ○ Mucinous
  - ○ Clear cell
  - ○ Mucoepidermoid
  - ○ Lymphoepithelioma-like
  - ○ Sarcomatous
- Perineural invasion is common

Precursor Lesions

- 2 types of precursor lesions
  - ○ Biliary intraepithelial neoplasia (BilIN)
  - – Flat or micropapillary proliferation of dysplastic epithelium
  - □ Divided into BilIN-1, 2, and 3 corresponding to low-, intermediate-, and high-grade dysplasia

○ Intraductal papillary neoplasm

– Noninvasive papillary biliary proliferation in dilated intrahepatic bile duct

DIFFERENTIAL DIAGNOSIS

Hepatocellular Carcinoma

- Positive for arginase-1, Hep-Par1, glypican-3, polyclonal CEA/CD10 (canalicular staining pattern), albumin in situ hybridization, CD34 (in sinusoidal endothelial cells)
- Bile production
- Negative mucin staining
- May have fat in tumor
- Tumor cells may contain Mallory-Denk bodies

Metastatic Adenocarcinoma

- Much more common in Western world
- Clinical history of primary carcinoma in other sites
- Immunoprofile may be helpful
- No underlying liver diseases or cirrhosis

Epithelioid Hemangioendothelioma

- Intracytoplasmic lumina, may contain red blood cells
- Positive for CD31, CD34, FLI-1, ERG

Combined Hepatocellular/Cholangiocarcinoma

- Has hepatocellular carcinoma component

Bile Ductular Reaction

- Abundant inflammation in clinical setting of biliary obstruction
  - Usually surrounded by neutrophils

Peribiliary Gland Hamartoma/Bile Duct Hamartoma (von Meyenburg Complex)

- Smaller and well circumscribed
- Lack of cytologic atypia
- May have angulated bile ducts

Atypical Reactive Bile Duct Epithelium

- Presence of marked background inflammation
- Lack of lymphovascular or perineural invasion
- Respects normal architecture of portal tracts

Biliary Adenofibroma

- Complex tubulocystic proliferation lined by biliary epithelium with no or minimal atypia
- Abundant fibrous stroma
- No mucin and no infiltrative growth pattern

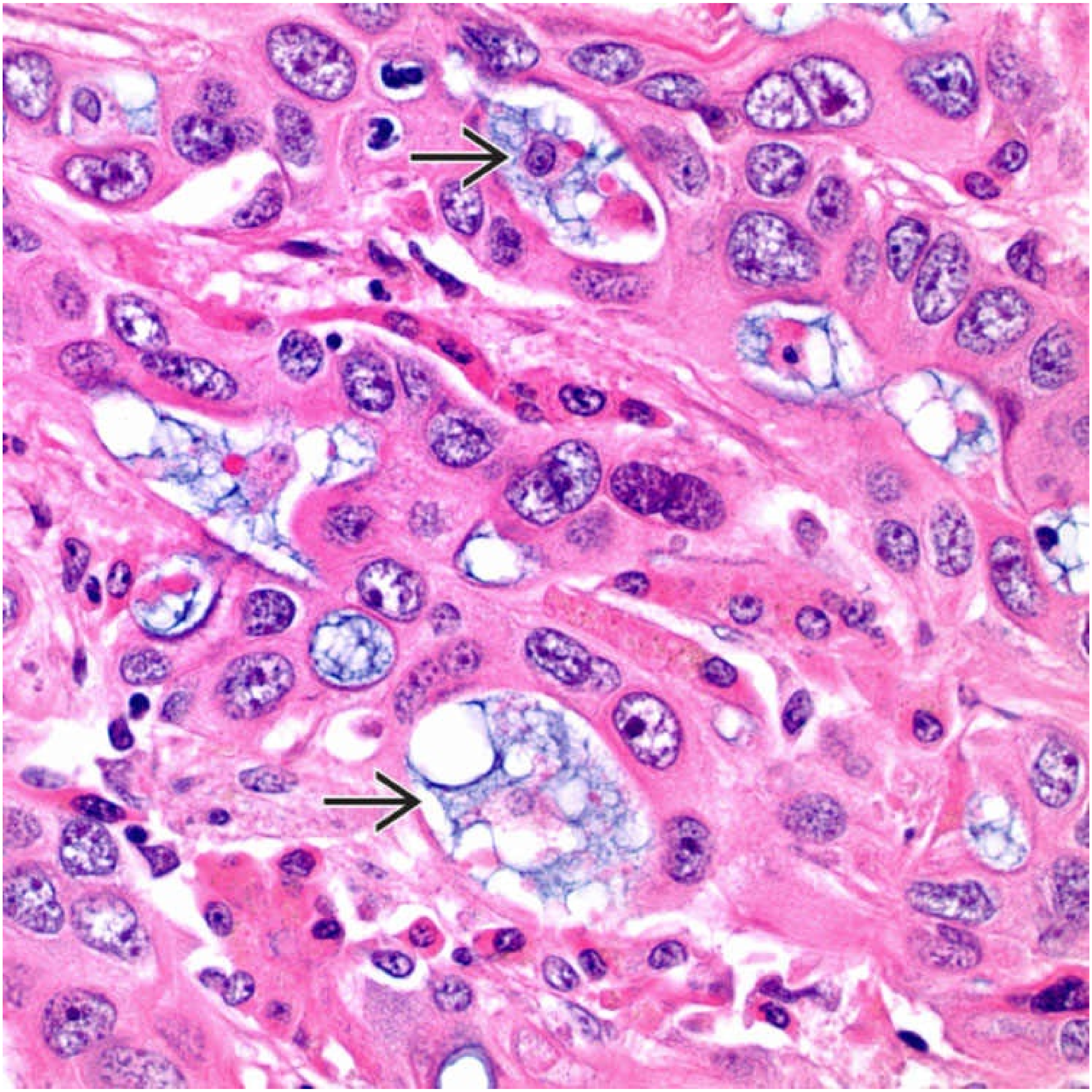
Hyperplasia of Peribiliary Glands

- Dilatation and hyperplasia of peribiliary glands that can be visible grossly
- Can occur in otherwise normal liver or in acquired liver diseases
- Alcohol-related liver disease associated with peribiliary cysts

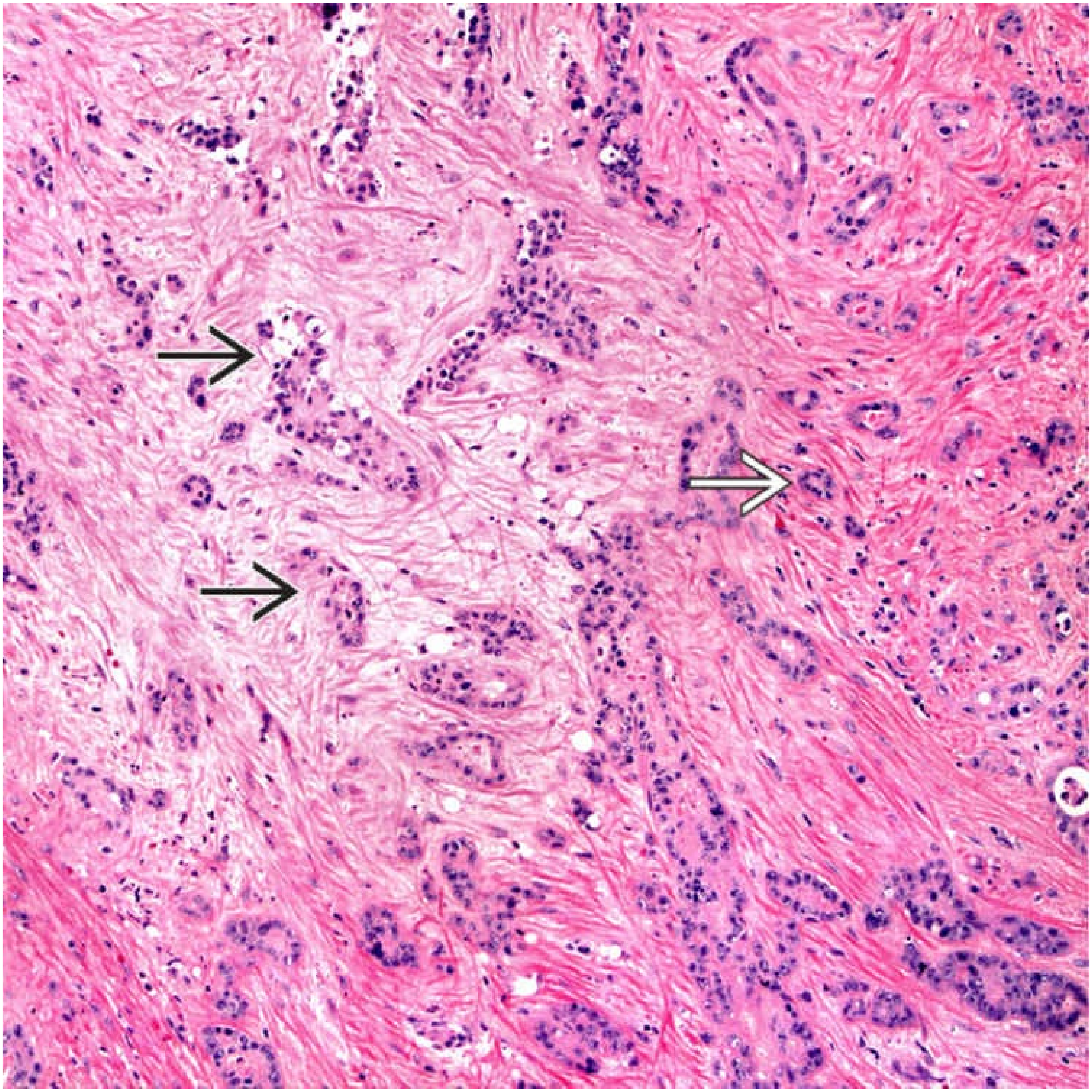
DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Immunophenotypic profiles of cholangiocarcinoma and pancreatic adenocarcinoma are virtually identical, and final distinction relies on clinical and imaging correlation

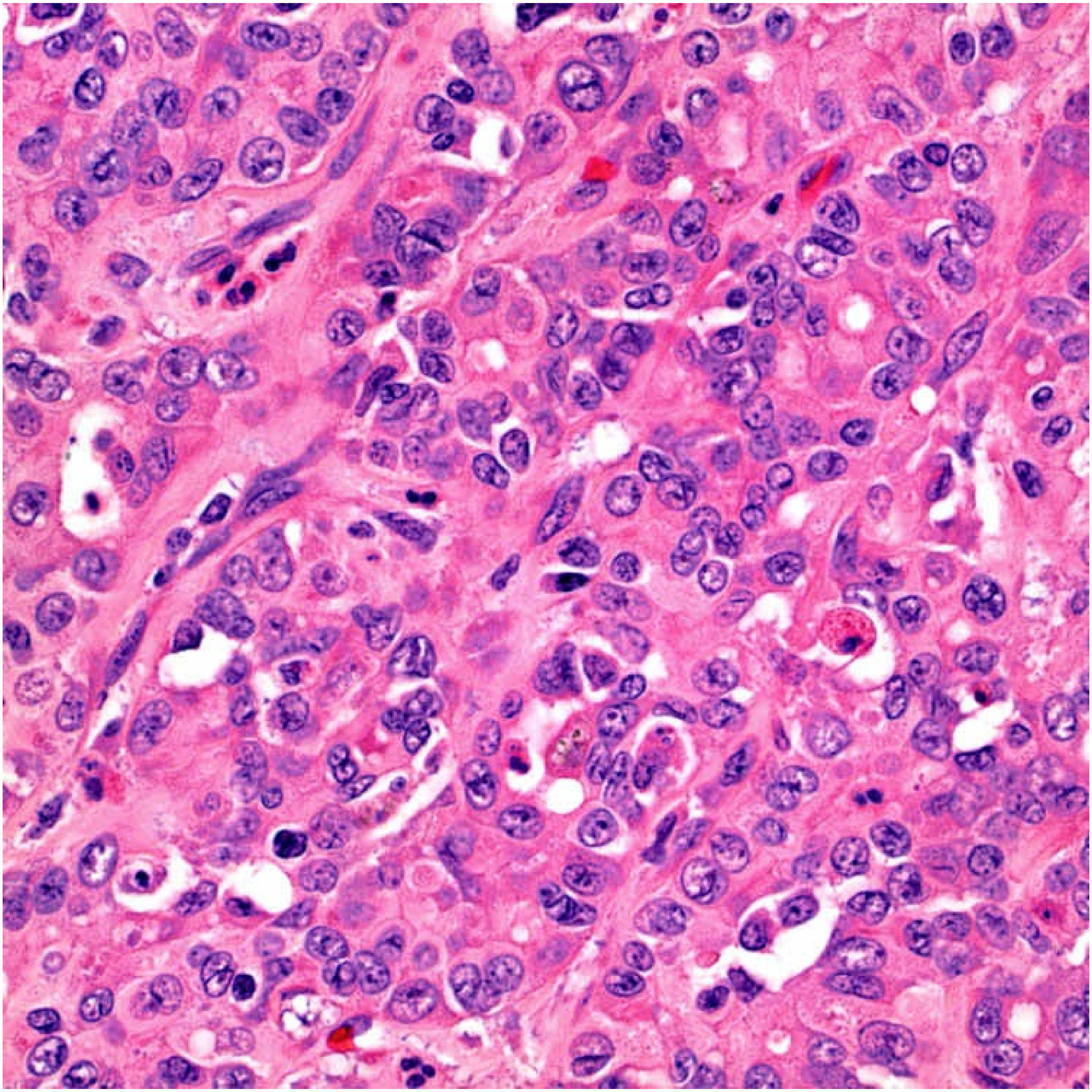


Mucin
Mucin is typically present → in the cytoplasm &/or the lumen.

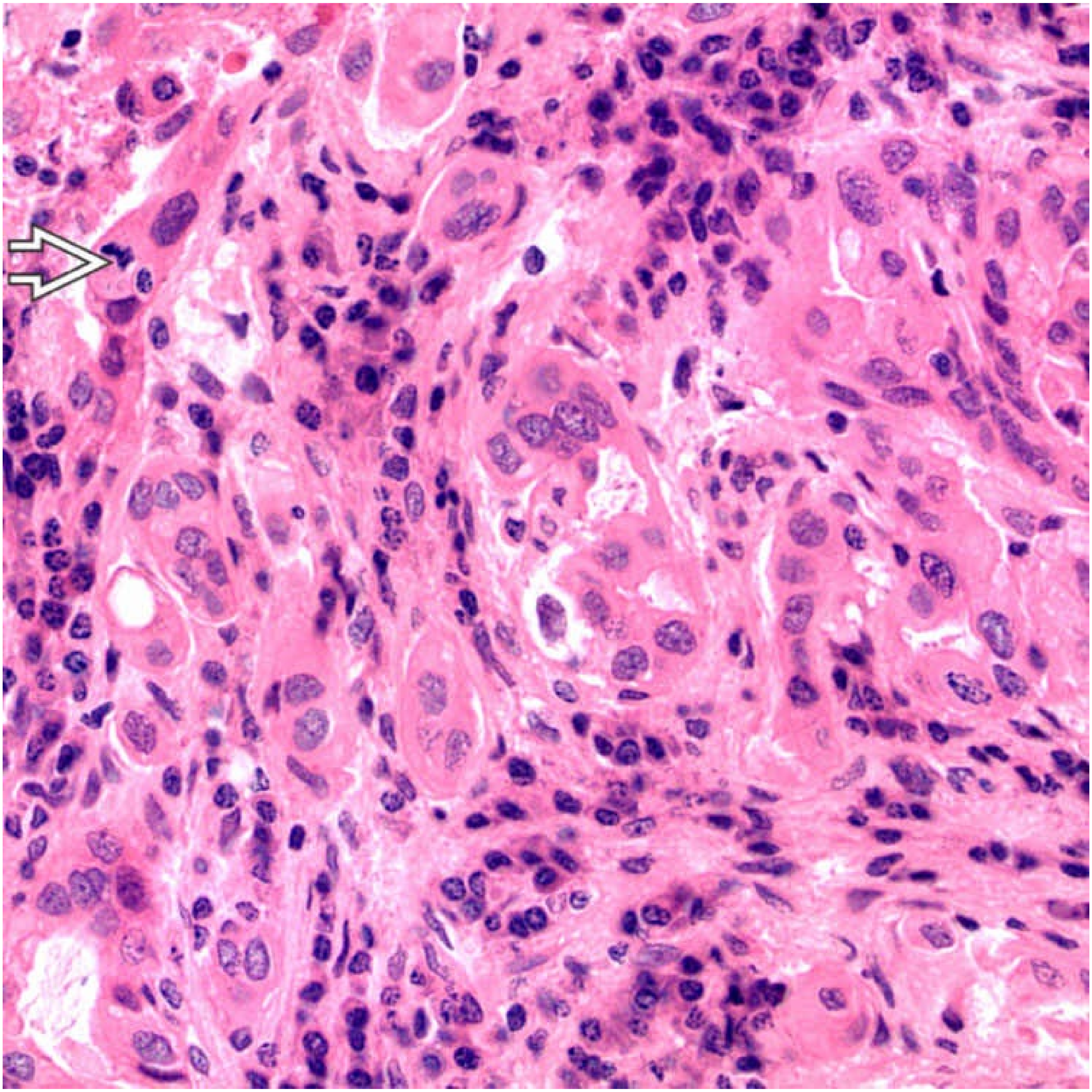


Well-Differentiated Appearance

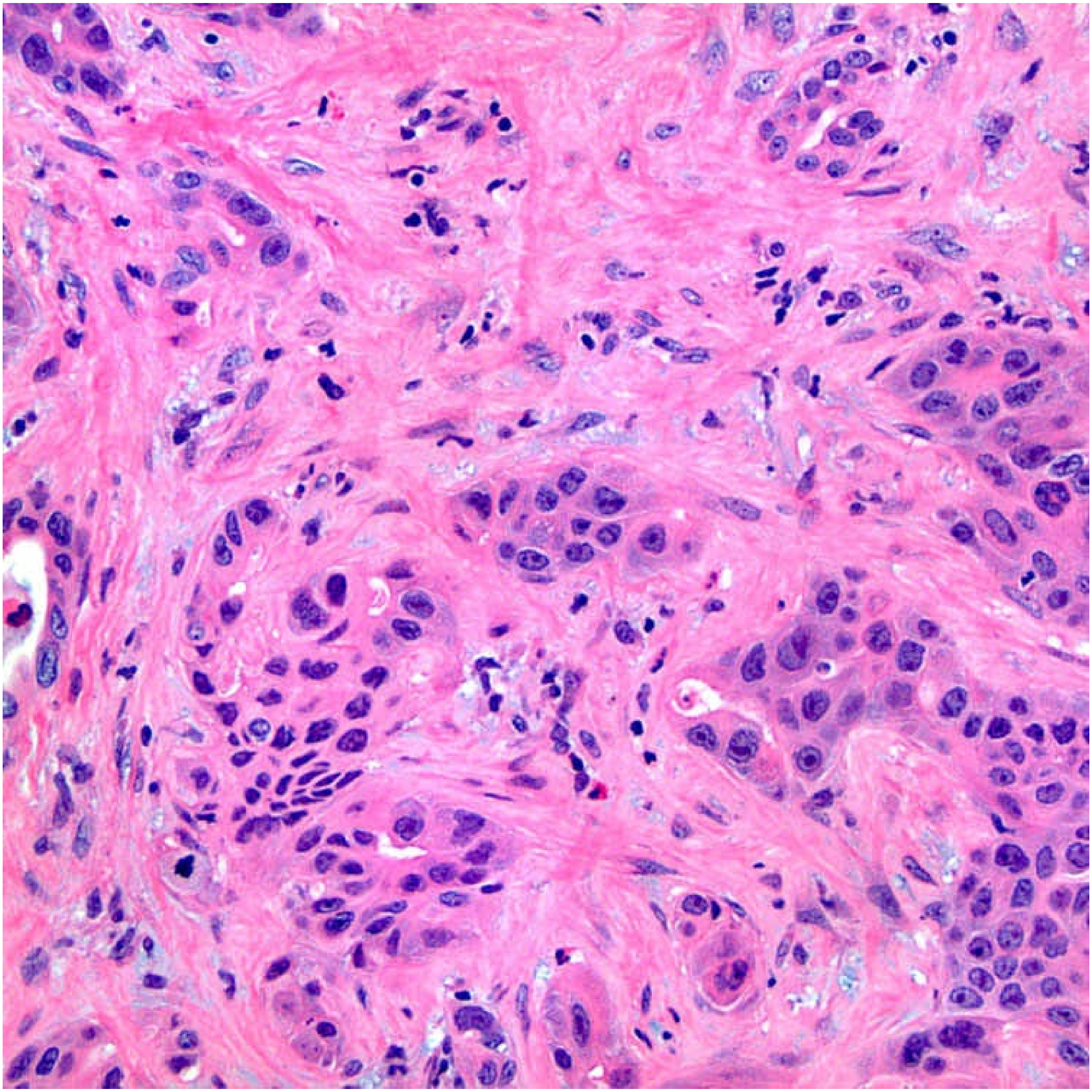
Well-formed neoplastic glands with minimal cytologic atypia → can be distinguished from benign bile ducts ⇒ by lack of normal lobular architecture, glandular crowding and complexity, and presence of desmoplastic stroma.



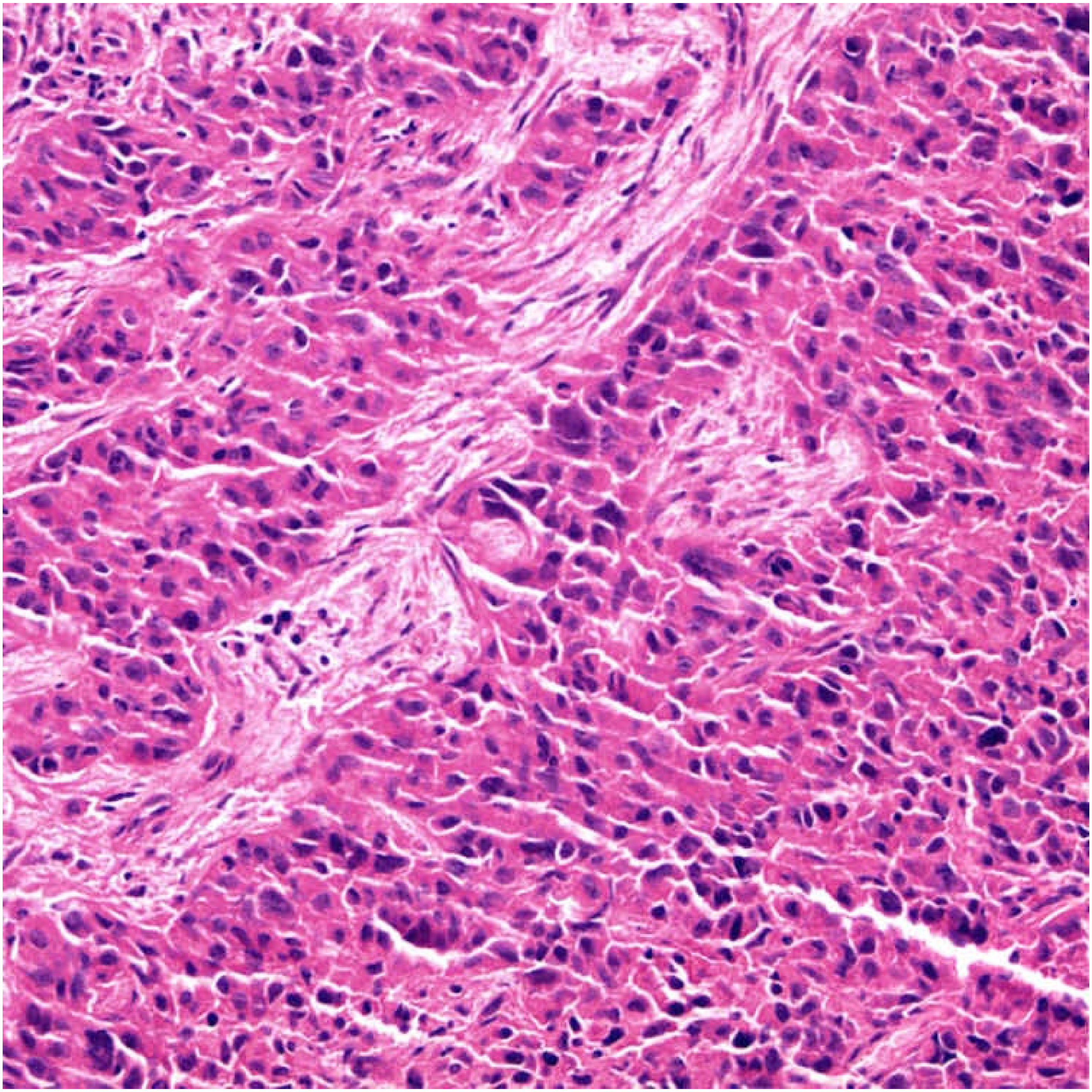
Moderately Differentiated Appearance
Crowded, back-to-back, small neoplastic glands with mild to moderate nuclear atypia are shown.



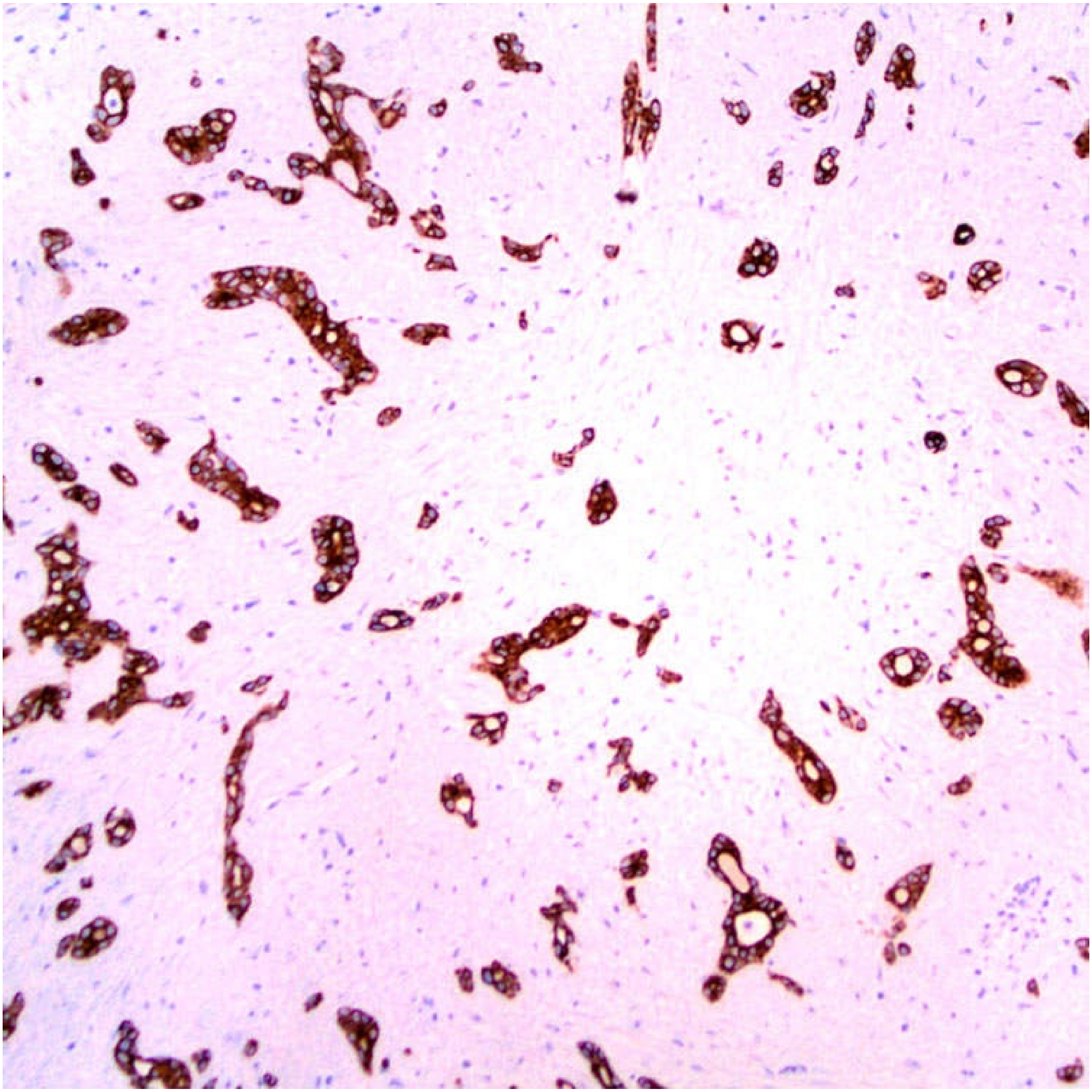
Irregular Glandular Structures of Cholangiocarcinoma
Closer view shows irregular glandular structures infiltrating in a prominent stroma. The nuclei are hyperchromatic and pleomorphic. Note the mitotic figure ⇨ .



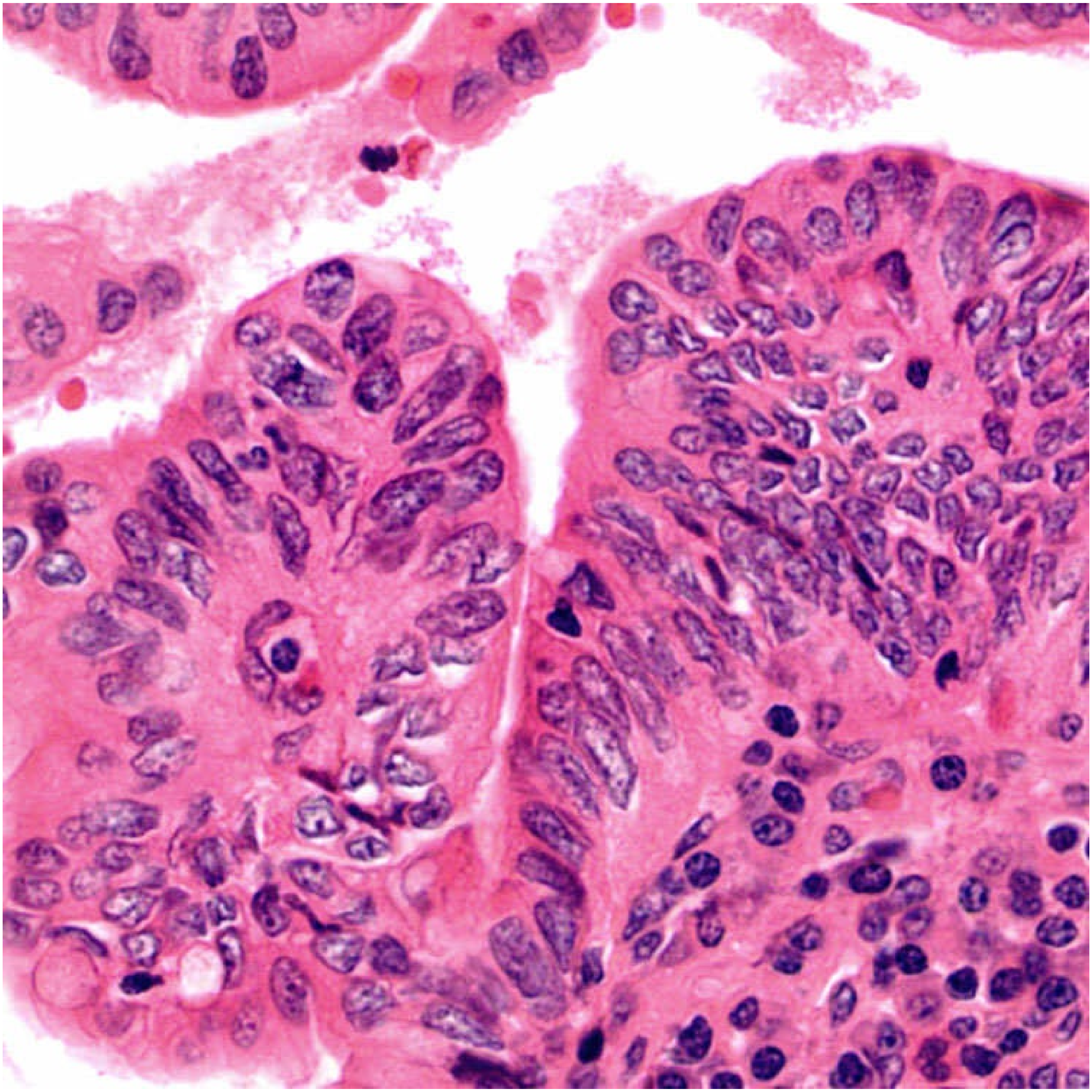
Prominent Stroma
Desmoplastic stroma is a common finding in these tumors.



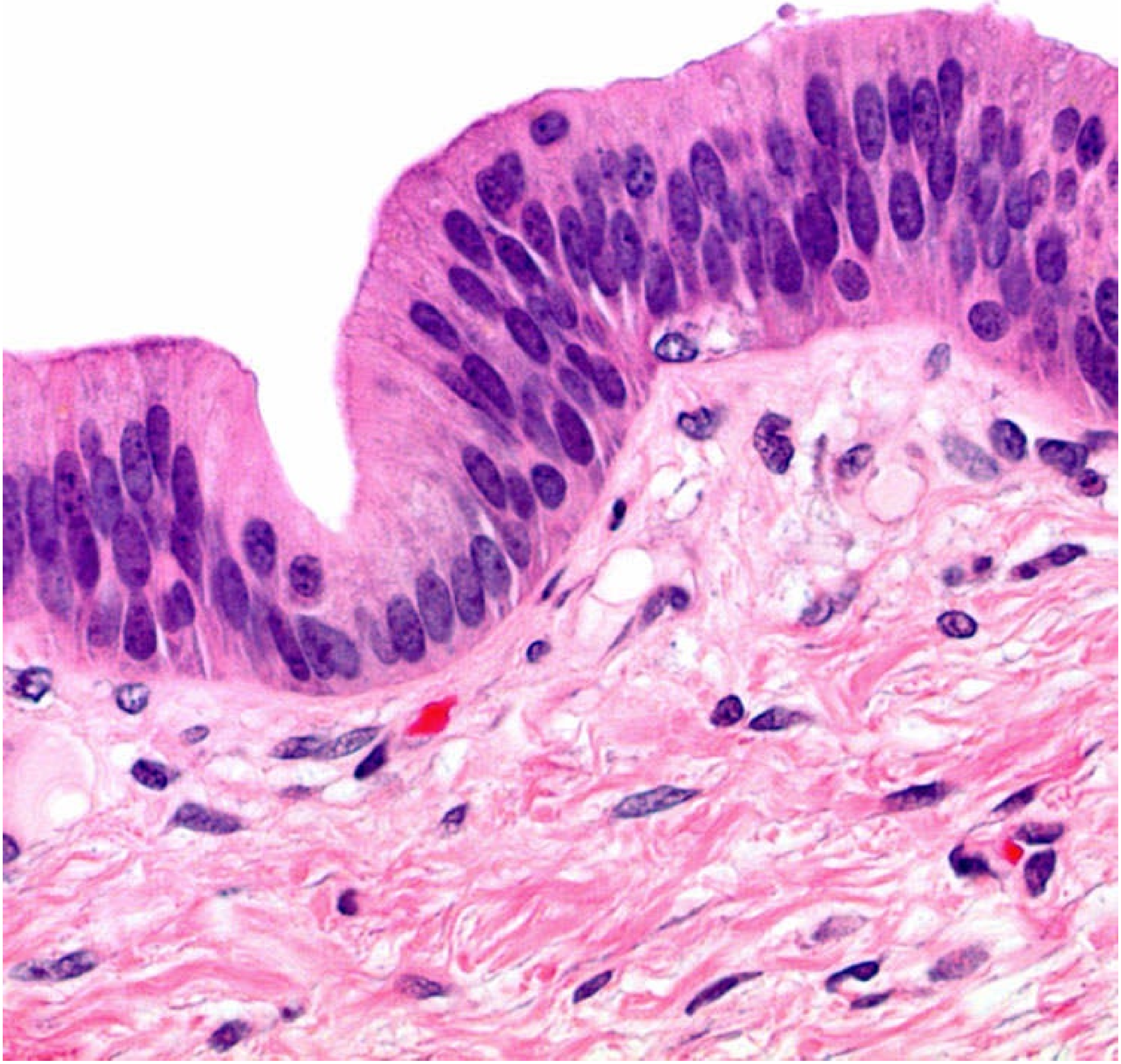
Poorly Differentiated
Solid sheets of tumor cells without obvious gland formation are shown. This can be difficult to distinguish from hepatocellular carcinoma without immunostains.



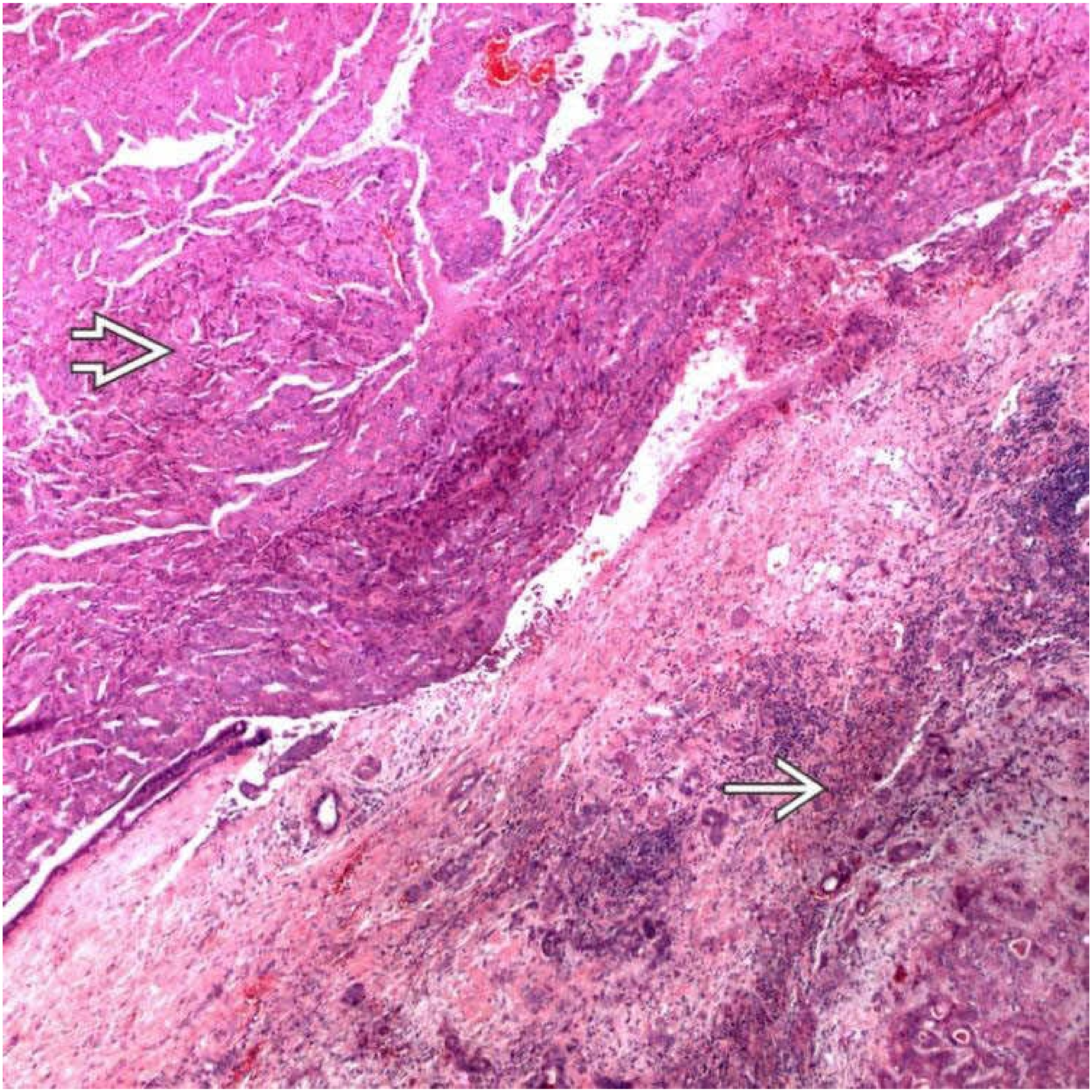
CK7 Stain
The infiltrating neoplastic glands are highlighted by CK7 immunostain.



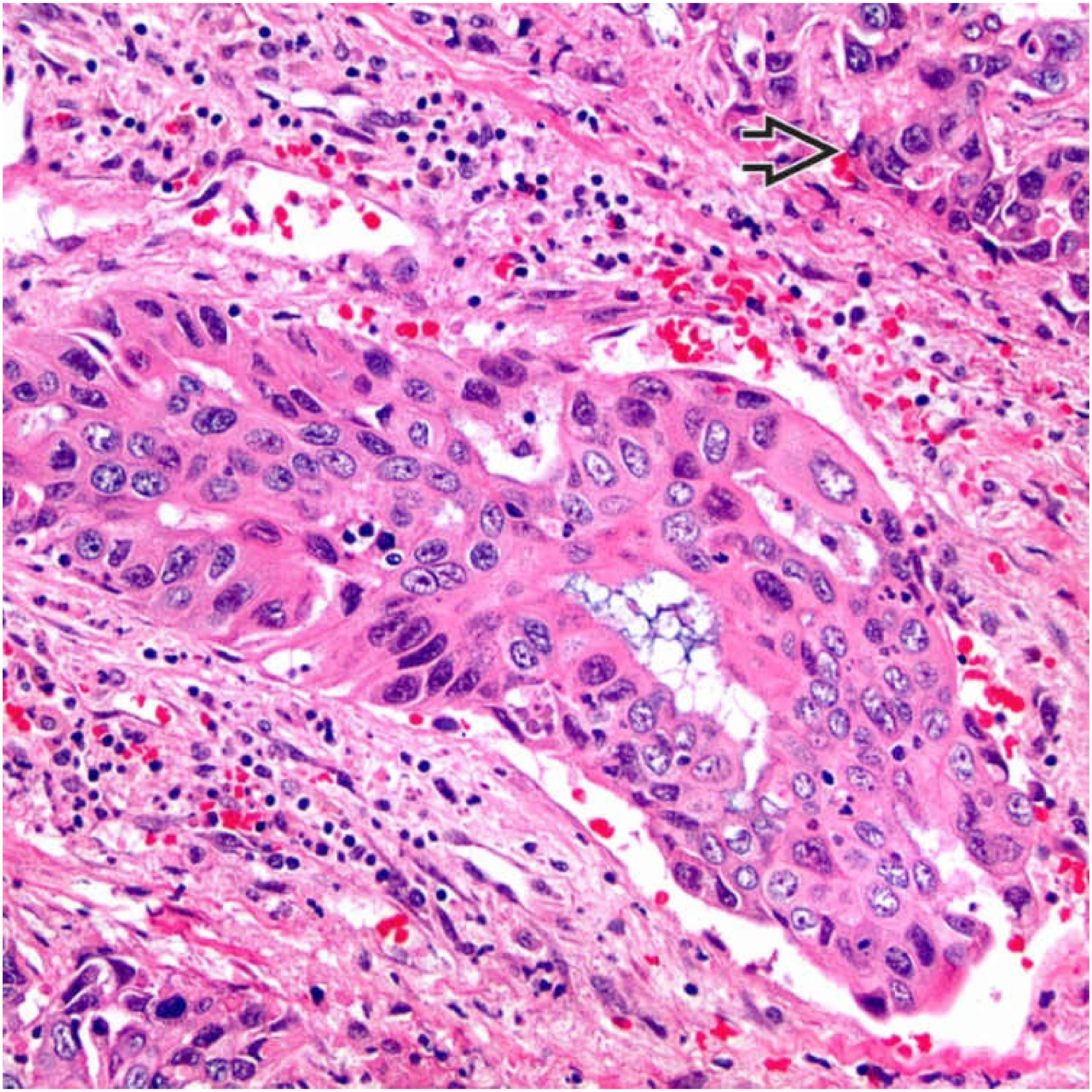
High-Grade Dysplasia
H&E shows intrahepatic bile duct adjacent to an intrahepatic cholangiocarcinoma with high-grade dysplasia characterized by cytologic atypia and loss of nuclear polarity.



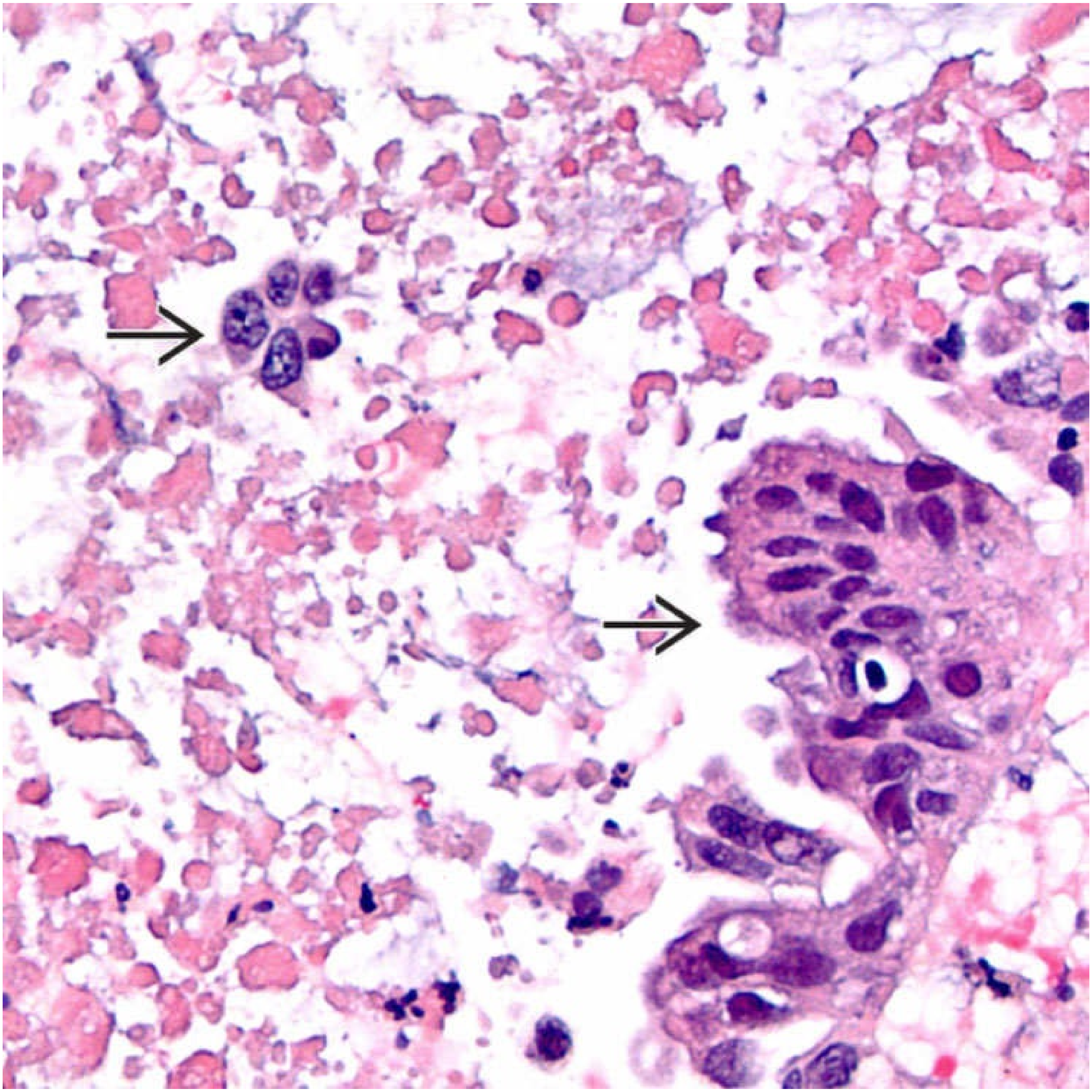
Low-Grade Dysplasia
Dysplastic epithelium in the intrahepatic bile ducts is considered to be a precursor lesion of intrahepatic cholangiocarcinoma.



Invasive Adenocarcinoma Arising in Intraductal Papillary Neoplasm of Bile Duct
Invasive adenocarcinoma ⇒ arising from intraductal papillary neoplasm of the bile duct ⇒ is shown.



High-Grade Dysplasia
High-grade dysplasia is shown in a large intrahepatic bile duct adjacent to invasive intrahepatic cholangiocarcinoma .



Fine-Needle Aspiration
Corresponding fine-needle aspiration → is shown.

SELECTED REFERENCES

1. Sato, Y, et al. Different carcinogenic process in cholangiocarcinoma cases epidemically developing among workers of a printing company in Japan. *Int J Clin Exp Pathol*. 2014; 7(8):4745–4754.

2. Schlitter, AM, et al. Intraductal papillary neoplasms of the bile duct: stepwise progression to

carcinoma involves common molecular pathways. *Mod Pathol*. 2014; 27(1):73–86.

3. Rizvi, S, et al. Pathogenesis, diagnosis, and management of cholangiocarcinoma. *Gastroenterology*. 2013; 145(6):1215–1229.
4. Pritchard, CC, et al. Pathology and diagnostic pitfalls of cholangiocarcinoma: Rising incidence of an old cancer. *Pathology Case Reviews*. 2009; 14:28–33.
5. Torbenson, M, et al. Bile duct dysplasia in the setting of chronic hepatitis C and alcohol cirrhosis. *Am J Surg Pathol*. 2007; 31(9):1410–1413.
6. Zen, Y, et al. Biliary intraepithelial neoplasia: an international interobserver agreement study and proposal for diagnostic criteria. *Mod Pathol*. 2007; 20(6):701–709.
7. Shaib, Y, et al. The epidemiology of cholangiocarcinoma. *Semin Liver Dis*. 2004; 24(2):115–125.
8. Tan, G, et al. Immunohistochemical analysis of biliary tract lesions. *Appl Immunohistochem Mol Morphol*. 2004; 12(3):193–197.
9. Lim, JH. Cholangiocarcinoma: morphologic classification according to growth pattern and imaging findings. *AJR Am J Roentgenol*. 2003; 181(3):819–827.
10. Lau, SK, et al. Comparative immunohistochemical profile of hepatocellular carcinoma, cholangiocarcinoma, and metastatic adenocarcinoma. *Hum Pathol*. 2002; 33(12):1175–1181.
11. Okuda, K, et al. Cholangiocarcinoma: recent progress. Part 1: epidemiology and etiology. *J Gastroenterol Hepatol*. 2002; 17(10):1049–1055.

Hemangioma

KEY FACTS

Terminology

- Most common primary tumor of liver
  - Incidence ranges from < 1% to 7.3% in autopsy studies

Clinical Issues

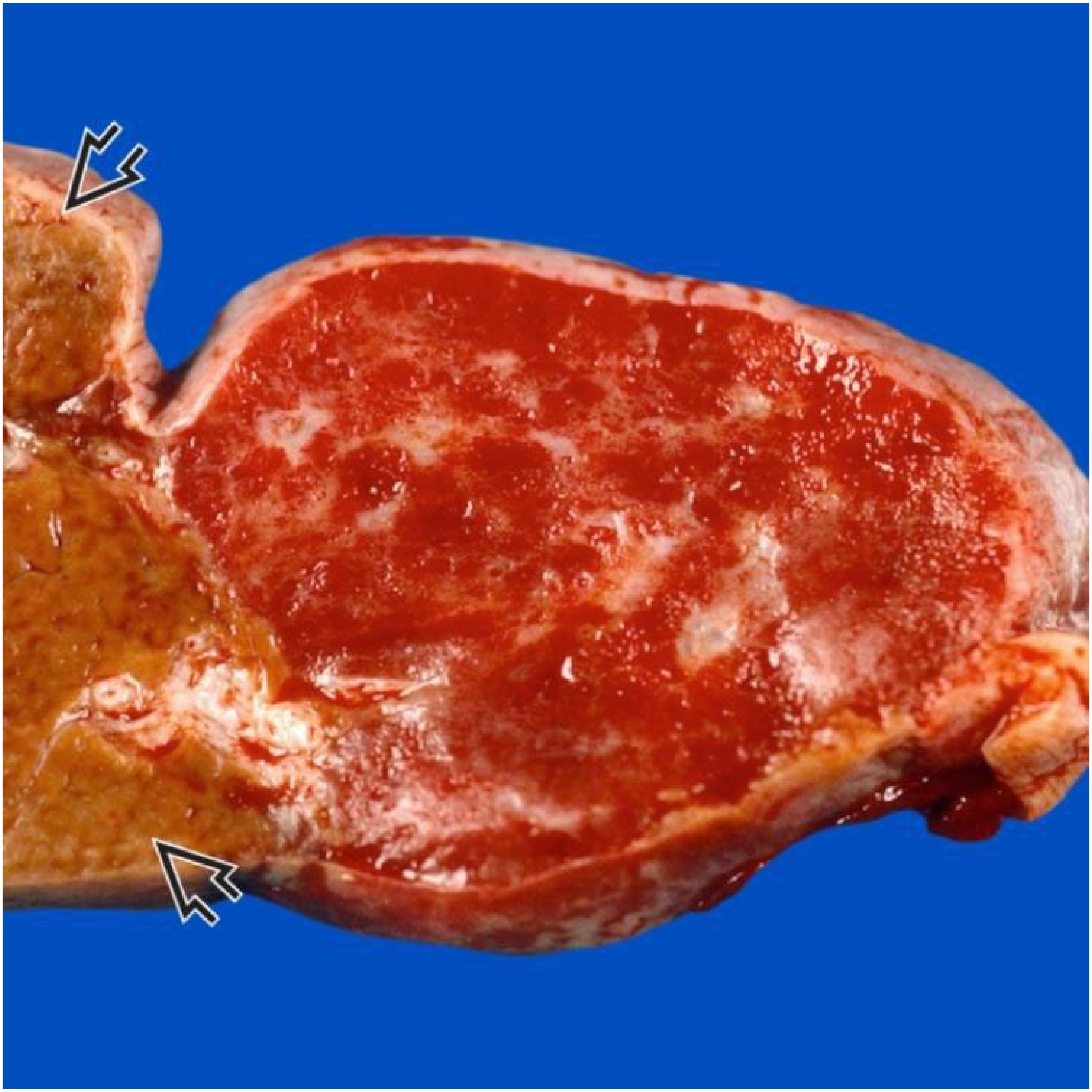
- Majority discovered incidentally
  - Clinically silent
    – Tumors under 4 cm rarely symptomatic
  - When symptomatic, present with abdominal pain, hepatomegaly, palpable mass
- More frequent in older patients and women
- Treatment is surgical resection or ablative therapy if symptomatic; otherwise observation
- Complications rare but include rupture and consumptive coagulopathy

Macroscopic

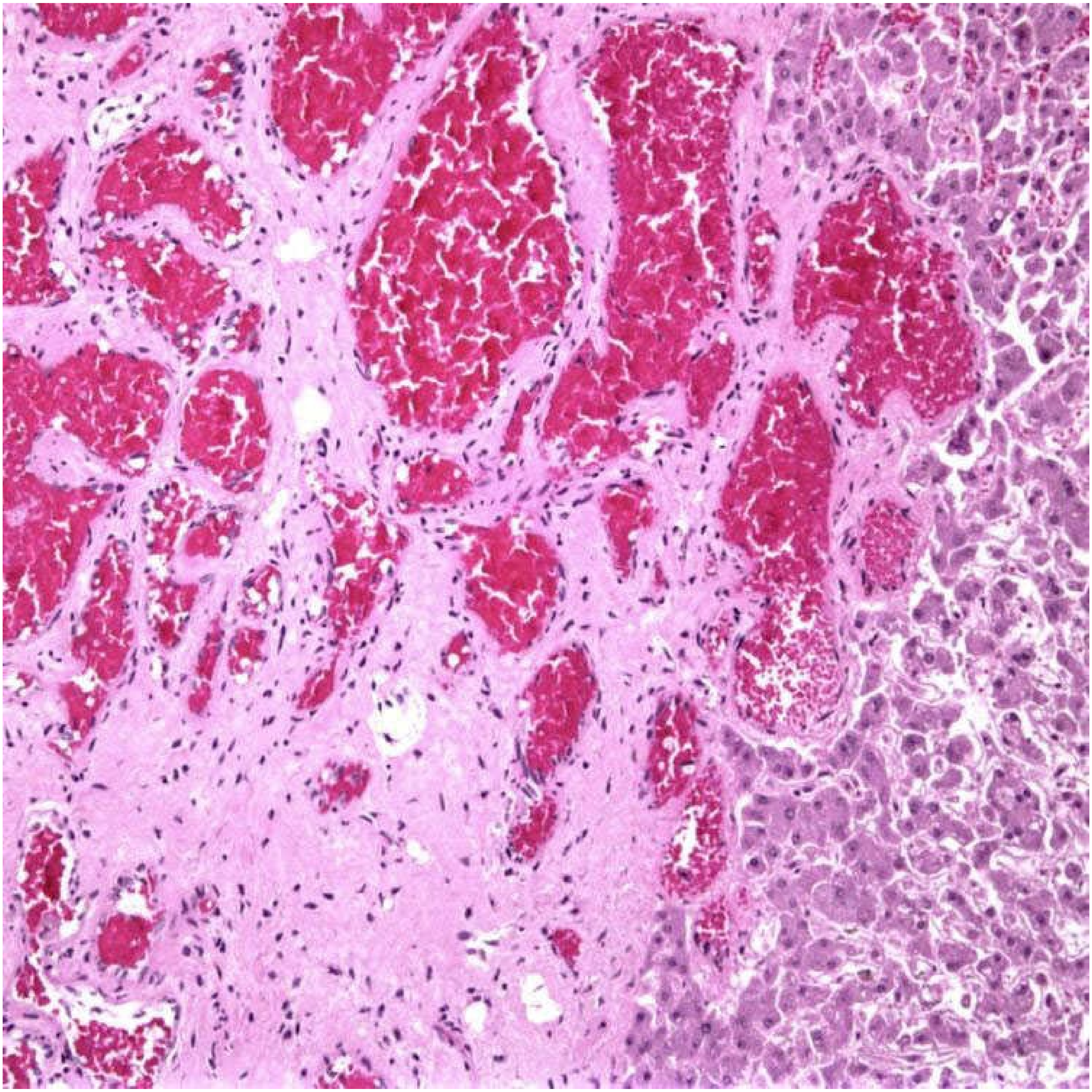
- Usually solitary and subcapsular
- Cut surface shows dark red, spongy mass composed of blood-filled cavities
- Most < 4 cm

Microscopic

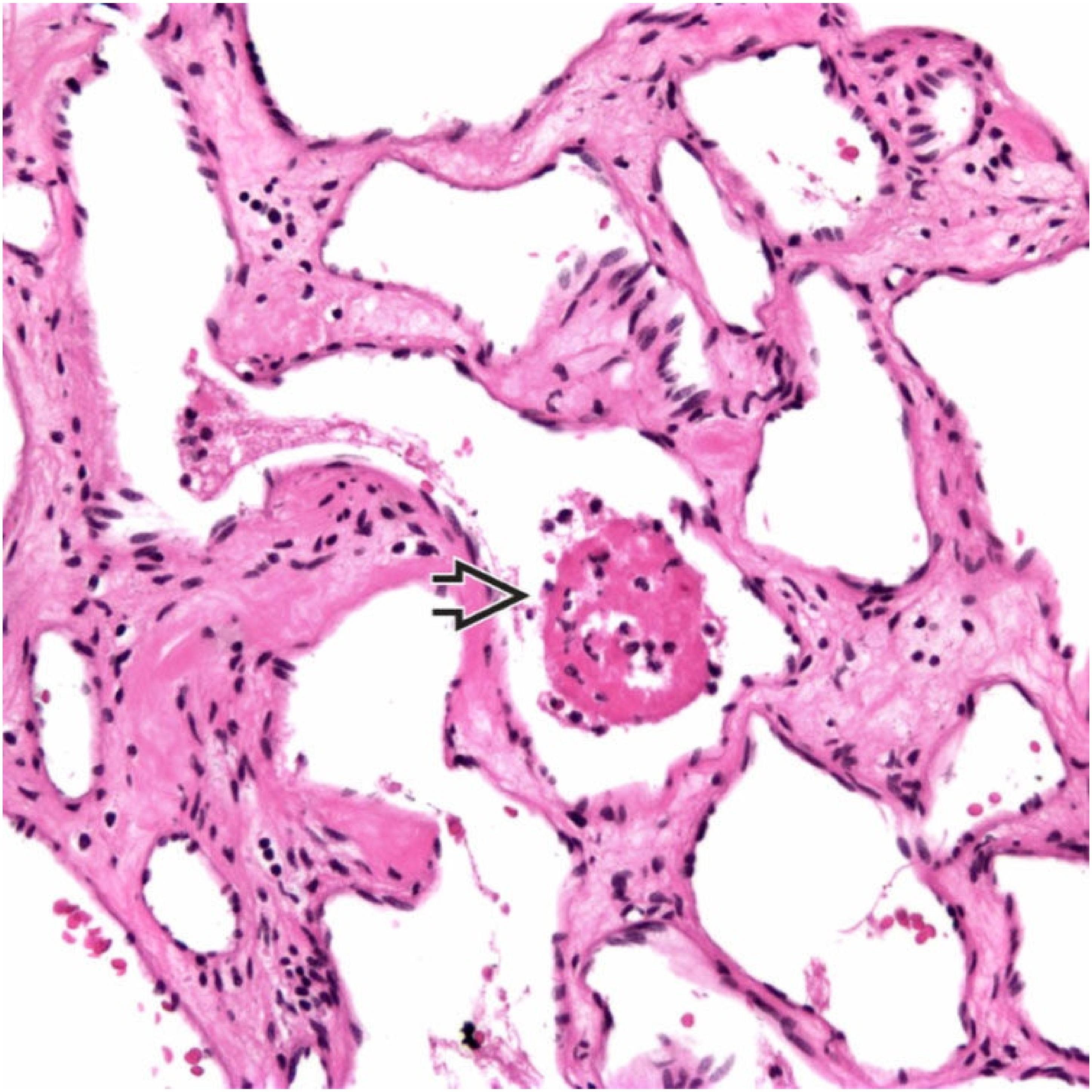
- Dilated, variably sized vascular spaces
  - Lined by flat, bland endothelial cells
  - Fibrin thrombi may be present in vascular spaces
- Connective tissue septa of varying widths
- Older lesions frequently contain involutional changes such as fibrosis, thrombosis, calcification
  - Can usually detect underlying vascular architecture even if involutional change is extensive



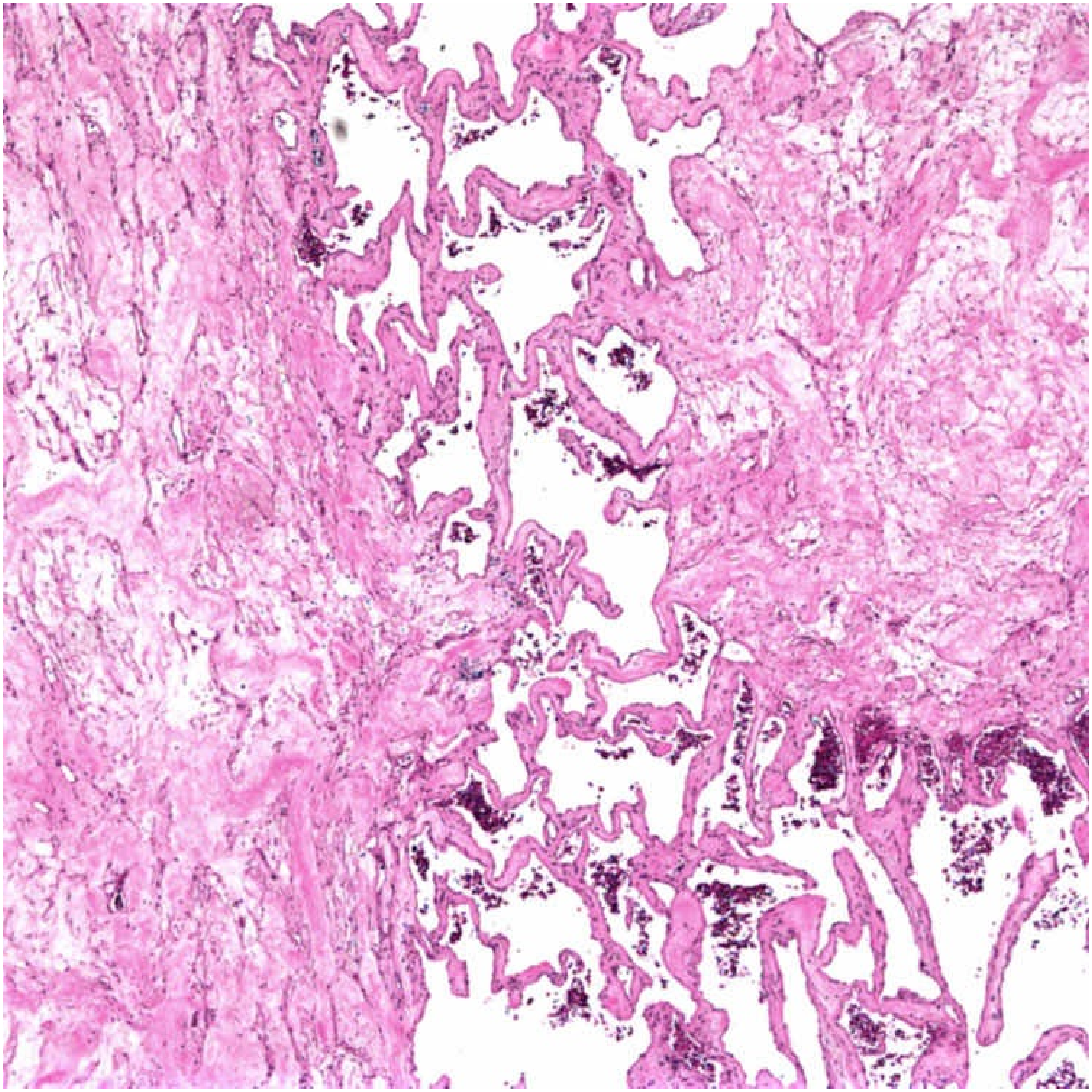
Gross Specimen
The cut surface of this partial hepatectomy specimen shows a spongy red mass directly beneath the capsule. Normal liver is to the left of the tumor ➩. (Courtesy G. Gray, MD.)



Dilated Vascular Channels Filled With Blood
This hemangioma has a somewhat irregular interface with the normal liver on the right. The lesion consists of dilated vascular channels filled with blood with intervening fibrous septa.



Dilated Vascular Spaces
Hemangiomas are composed of dilated vascular spaces with a bland, flat endothelial lining. The intervening fibrous bands are paucicellular and of varying thickness. Note the organizing thrombus in a vascular space ➪ .



Fibrosis

This hemangioma shows marked fibrosis, a common involutional change due to thrombosis over time. Residual typical dilated vascular channels are seen in the center of the picture.

TERMINOLOGY

Synonyms

- Cavernous hemangioma, sclerosing hemangioma

Definitions

- Benign vascular tumor

- Most common primary tumor of liver

ETIOLOGY/PATHOGENESIS

Unknown

- Possibly congenital
- Postulated but unproven role of sex hormones

CLINICAL ISSUES

Epidemiology

- Incidence
  - Ranges from < 1% to 7.3% in autopsy studies
- Age
  - All ages
    - More frequent in older patients
- Sex
  - More common in women
    - May be that hemangiomas are larger and more often symptomatic in women, so more likely to be diagnosed

Presentation

- Majority discovered incidentally during imaging for some other reason
  - Clinically silent
  - Tumors under 4 cm rarely symptomatic
- Larger tumors may be symptomatic
- Vague abdominal pain, hepatomegaly, palpable mass
- Complications rare
  - Spontaneous rupture
  - Consumptive coagulopathy

Treatment

- Surgical resection or ablative therapy if symptomatic; otherwise observation

Prognosis

- Excellent

IMAGING

MR Findings

- Heterogeneous appearance that is virtually diagnostic
  - Hemangiomas with extensive scarring may mimic other tumors, such as cholangiocarcinoma

MACROSCOPIC

General Features

- Usually solitary
  - 10% or less are multiple
- Usually subcapsular
  - May appear as red or purple capsular blotches
- Cut surface shows dark red, spongy mass composed of blood-filled cavities
  - Variably present scarring, calcification
- Occurs anywhere in liver
- Involuted lesions may consist mostly of fibrosis, calcification, &/or necrosis

Size

- Most < 4 cm
  - Tumors up to 30 cm have been described

MICROSCOPIC

Histologic Features

- Well demarcated from surrounding liver
  - Occasional irregular interface
- Dilated, variably sized vascular spaces
  - Spaces lined by flat, bland endothelial cells
    - No endothelial atypia
  - Connective tissue septa
    - Paucicellular fibrous bands of varying width
    - Variably present fibrosis and myxoid change
    - Larger septa may contain thick-walled vessels, bile ducts
  - Fibrin thrombi may be present in vascular spaces
- Older lesions frequently contain involutional changes
  - Hyalinization
  - Thrombosis
  - Obliteration of vascular channels
  - Calcification or ossification
  - Necrosis
  - Can usually detect underlying vascular architecture even if involutional change is extensive

DIFFERENTIAL DIAGNOSIS

Peliosis Hepatis

• No fibrous septa

Hereditary Hemorrhagic Telangiectasia

• Dilated vascular channels are in portal tracts and periportal zones
• Accompanied by aberrant portal vessels

Infantile Hemangioendothelioma

• Characteristic small vascular proliferation

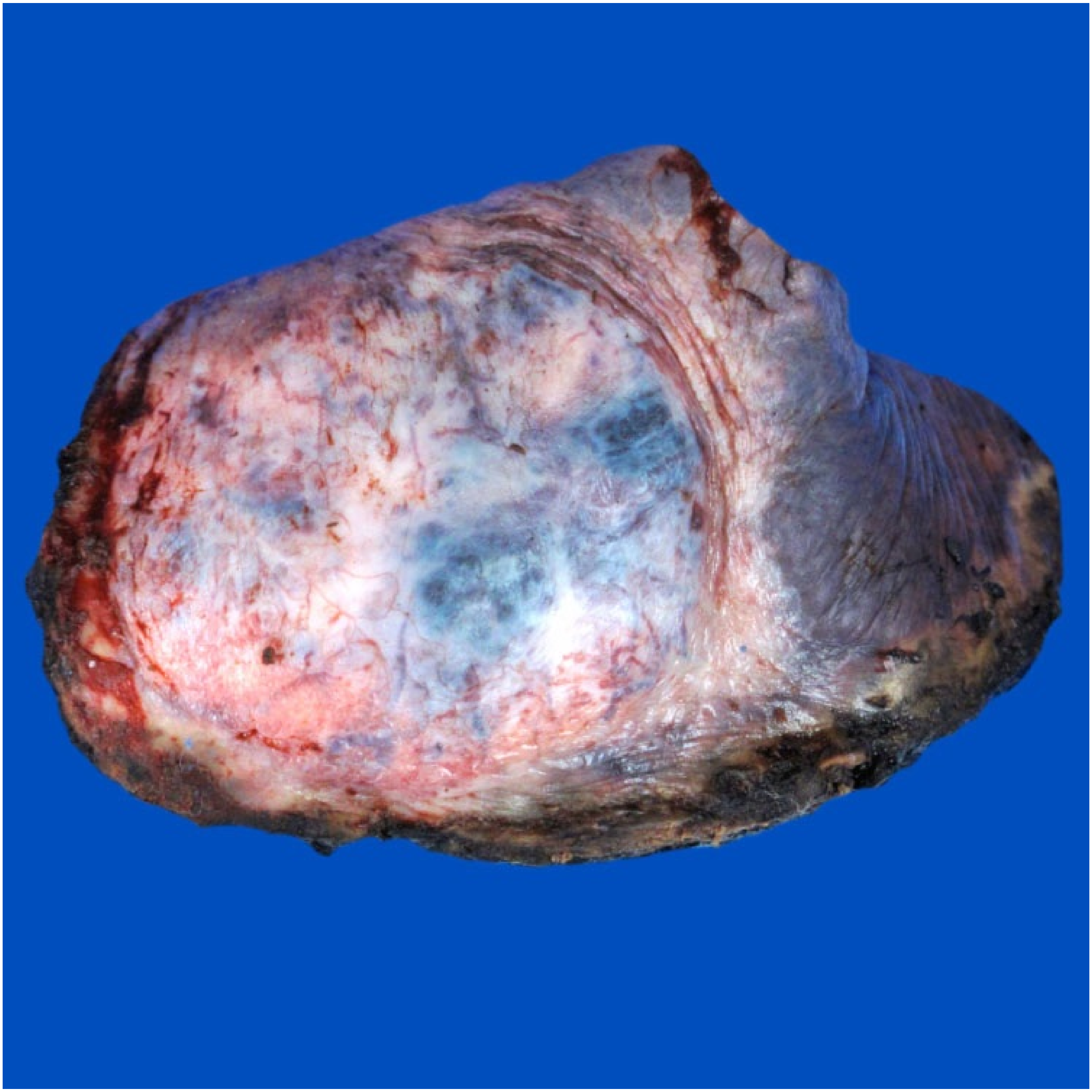
Angiosarcoma

• Malignant endothelial cells

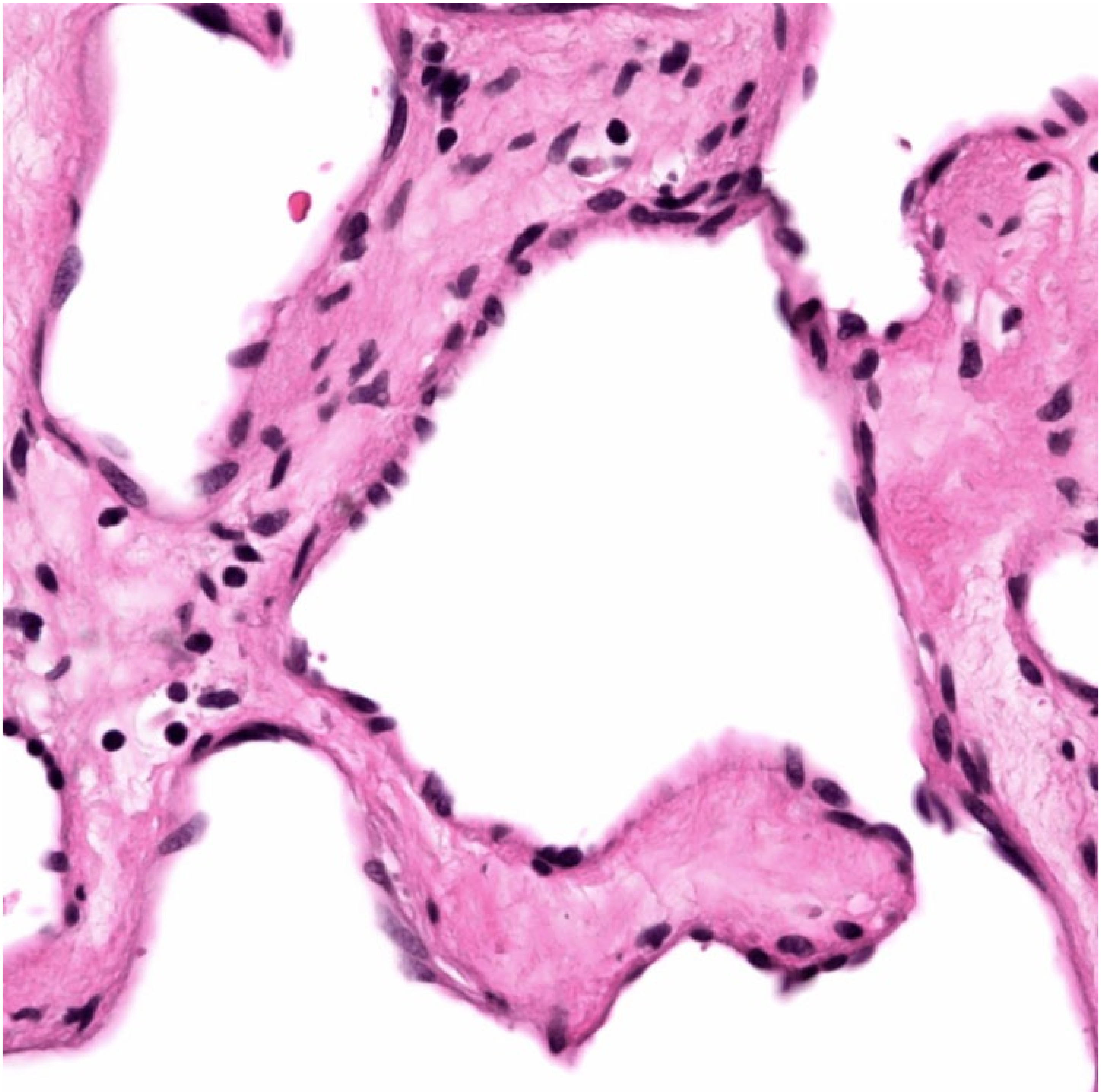
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

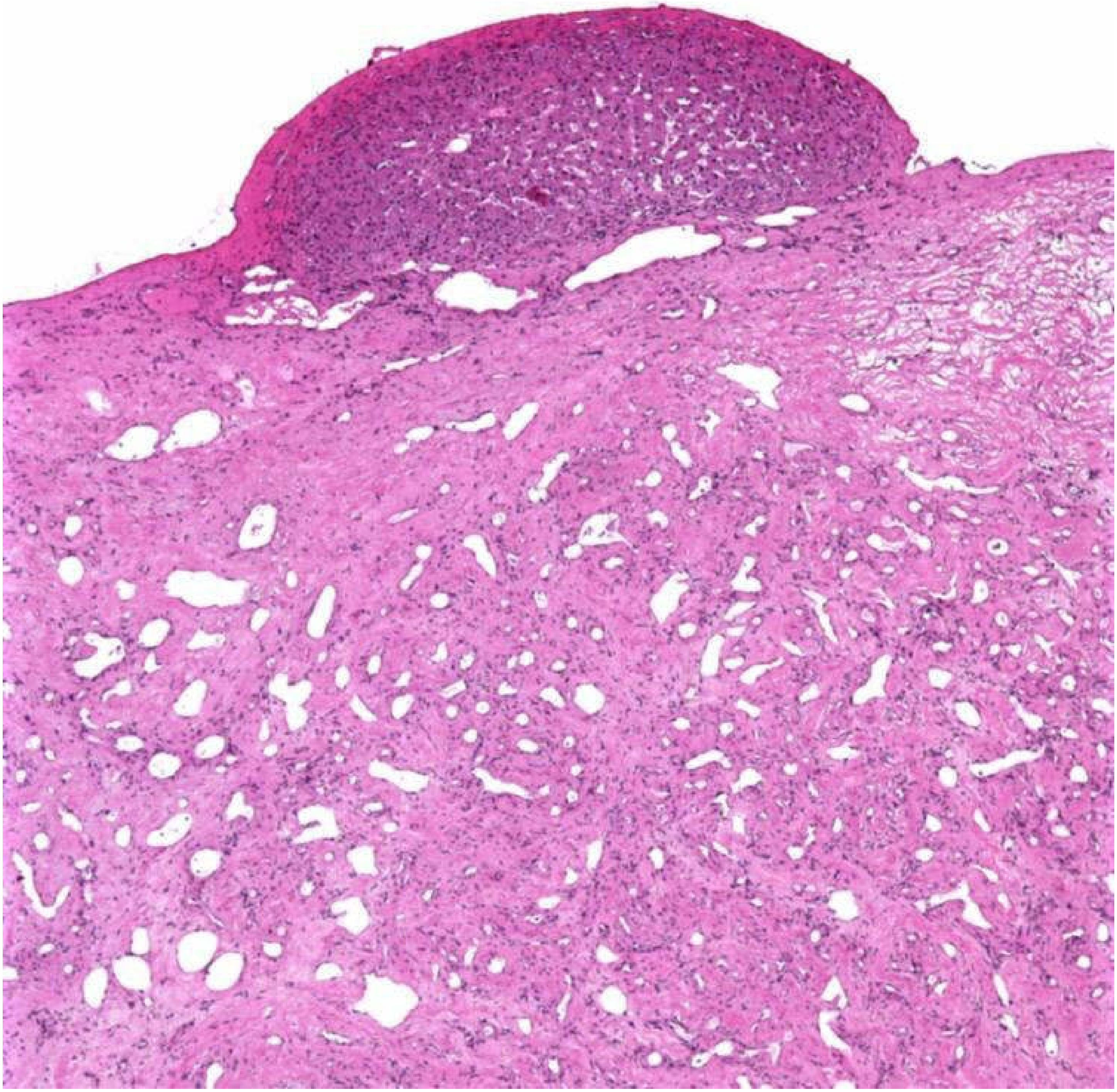
• Core needle biopsy contraindicated because of bleeding risk; FNA usually safe



This photograph illustrates a typical subcapsular hemangioma with extensive fibrosis and hemorrhage on the cut surface. (Courtesy S. Sharma, MD.)



The vascular spaces in hemangiomas are lined by bland, flat endothelial cells without any atypia.



Over time, some lesions show much more fibrosis and fewer dilated, blood-filled spaces.

SELECTED REFERENCES

1. Semaan, A, et al. Incidentally detected focal liver lesions – a common clinical management dilemma revisited. *Anticancer Res*. 2016; 36(6):2923–2932.
2. Bajenaru, N, et al. Hepatic hemangioma -review-. *J Med Life*. 2015; 8 Spec Issue:4–11.
3. Miyamoto, S, et al. Hepatic sclerosed hemangioma: a case report and review of the literature. *BMC Surg*. 2015; 15:45.
4. Toro, A, et al. What is changing in indications and treatment of hepatic hemangiomas. A review. *Ann Hepatol*. 2014; 13(4):327–339.
5. Glinkova, V, et al. Hepatic haemangiomas: possible association with female sex hormones. *Gut*.

2004; 53(9):1352–1355.

6. Gandolfi, L, et al. Natural history of hepatic haemangiomas: clinical and ultrasound study. *Gut*. 1991; 32(6):677–680.
7. Schwartz, SI, et al. Cavernous hemangioma of the liver. A single institution report of 16 resections. *Ann Surg*. 1987; 205(5):456–465.
8. Karhunen, PJ. Benign hepatic tumours and tumour like conditions in men. *J Clin Pathol*. 1986; 39(2):183–188.
9. Berry, CL. Solitary “necrotic nodule” of the liver: a probable pathogenesis. *J Clin Pathol*. 1985; 38(11):1278–1280.
10. Trastek, VF, et al. Cavernous hemangiomas of the liver: resect or observe? *Am J Surg*. 1983; 145(1):49–53.

Angiomyolipoma

KEY FACTS

Terminology

- Rare, benign mesenchymal neoplasm composed of smooth muscle, adipose tissue, and vessels
- Thought to arise from perivascular epithelioid cells (PEC); therefore, considered part of PEComa family of tumors

Clinical Issues

- Infrequently associated with tuberous sclerosis (6-10%)
- Benign behavior in nearly all cases
- Most patients are asymptomatic and present incidentally

Microscopic

- Tumor consists of 3 elements in varying proportions: Fat, abnormal vessels, myoid cells
  - Diagnostic component is spindle or epithelioid smooth muscle cells
  - Epithelioid smooth muscle cells are typically large, with round to oval nuclei, and eosinophilic to fibrillar or vacuolated cytoplasm
- Features that predict malignant behavior are not well defined
  - Nuclear atypia and infiltrative margins can be seen in benign tumors

Ancillary Tests

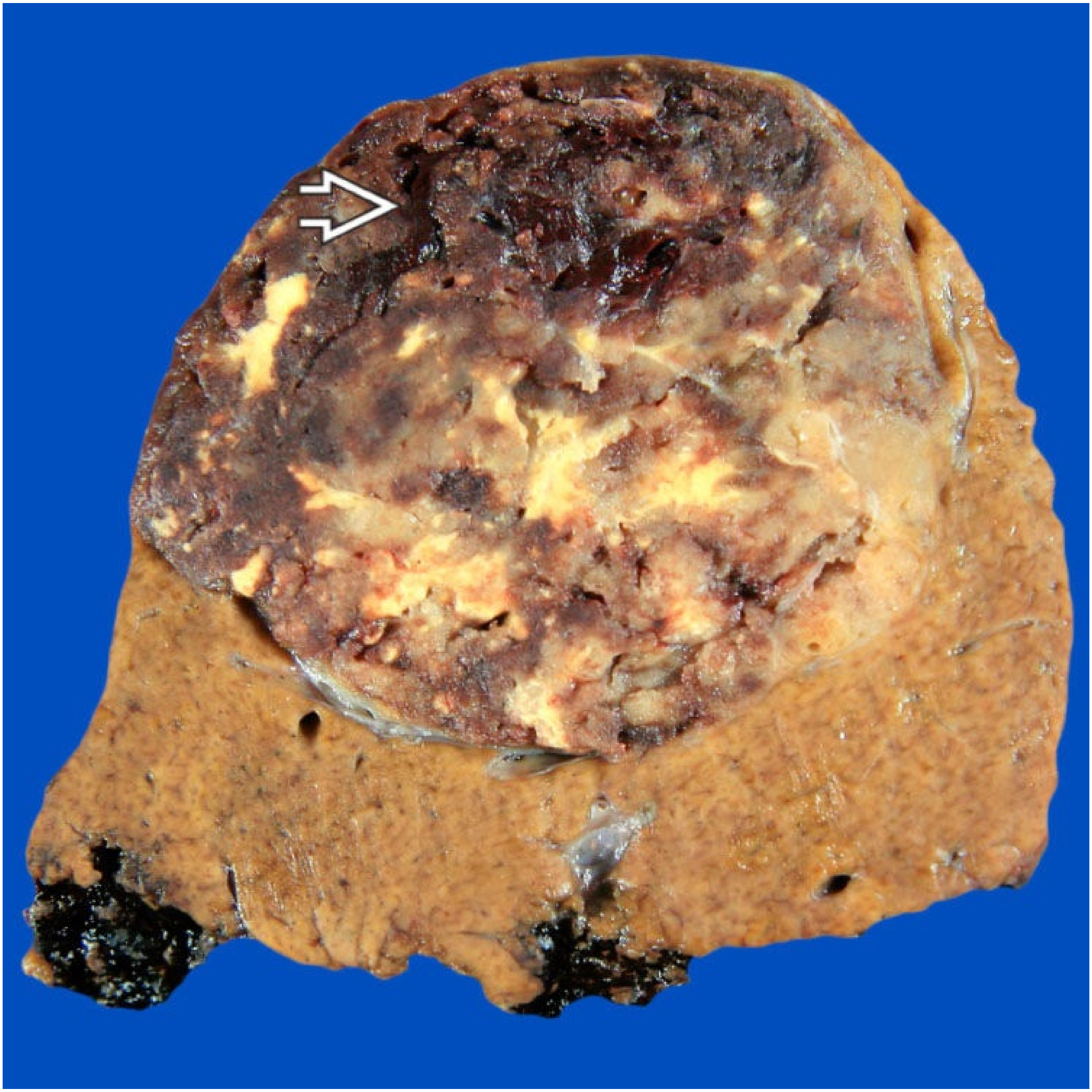
- Smooth muscle cells stain with antibodies to HMB-45, MART-1, but not keratin or Hep-Par1

Top Differential Diagnoses

- Hepatocellular neoplasm, particularly hepatocellular carcinoma
- Metastatic malignant tumor, either carcinoma or sarcoma
- Malignant melanoma

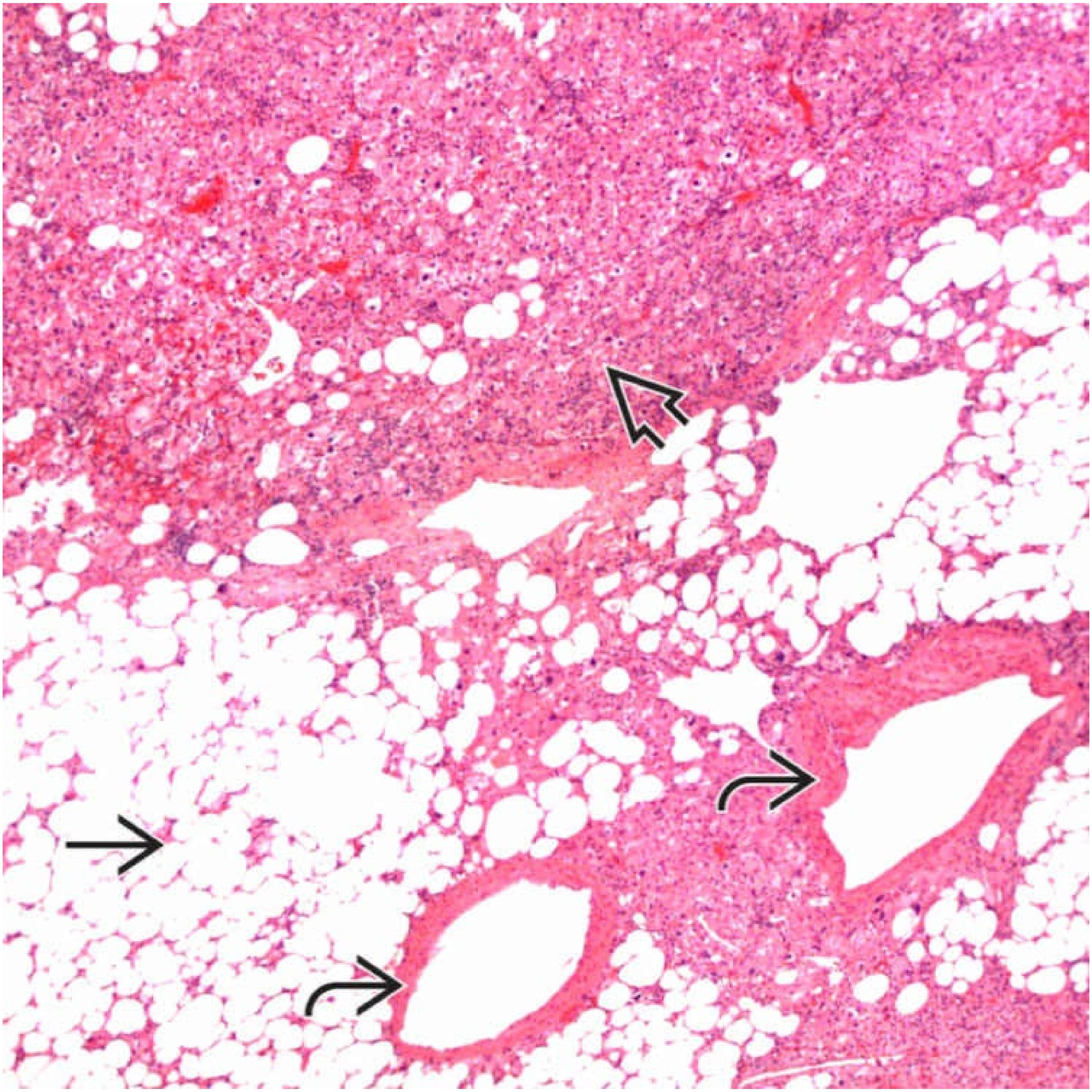
Diagnostic Checklist

- Heterogeneous tumor that contains mixture of plump eosinophilic cells and fat should raise suspicion for angiomyolipoma

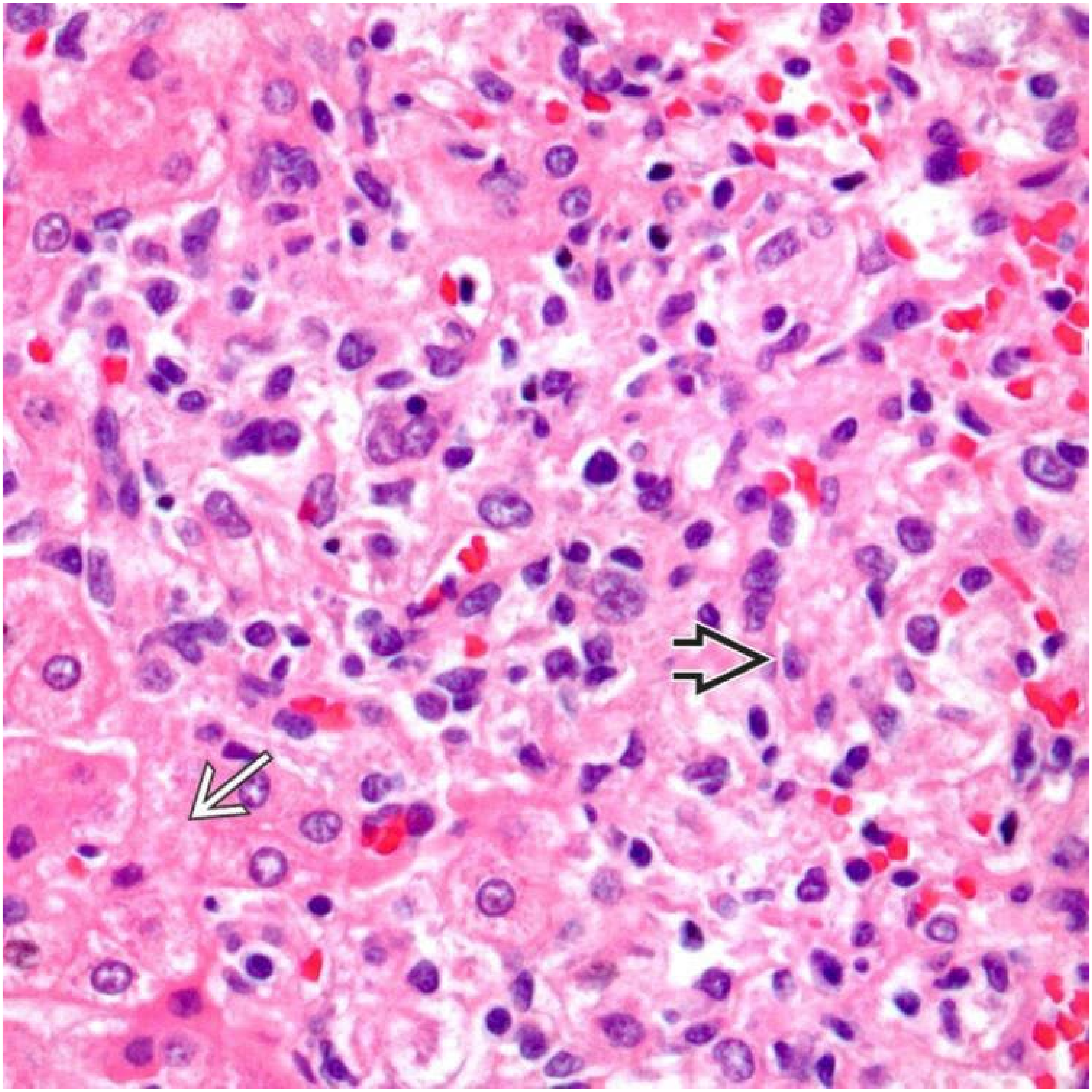


Gross Appearance

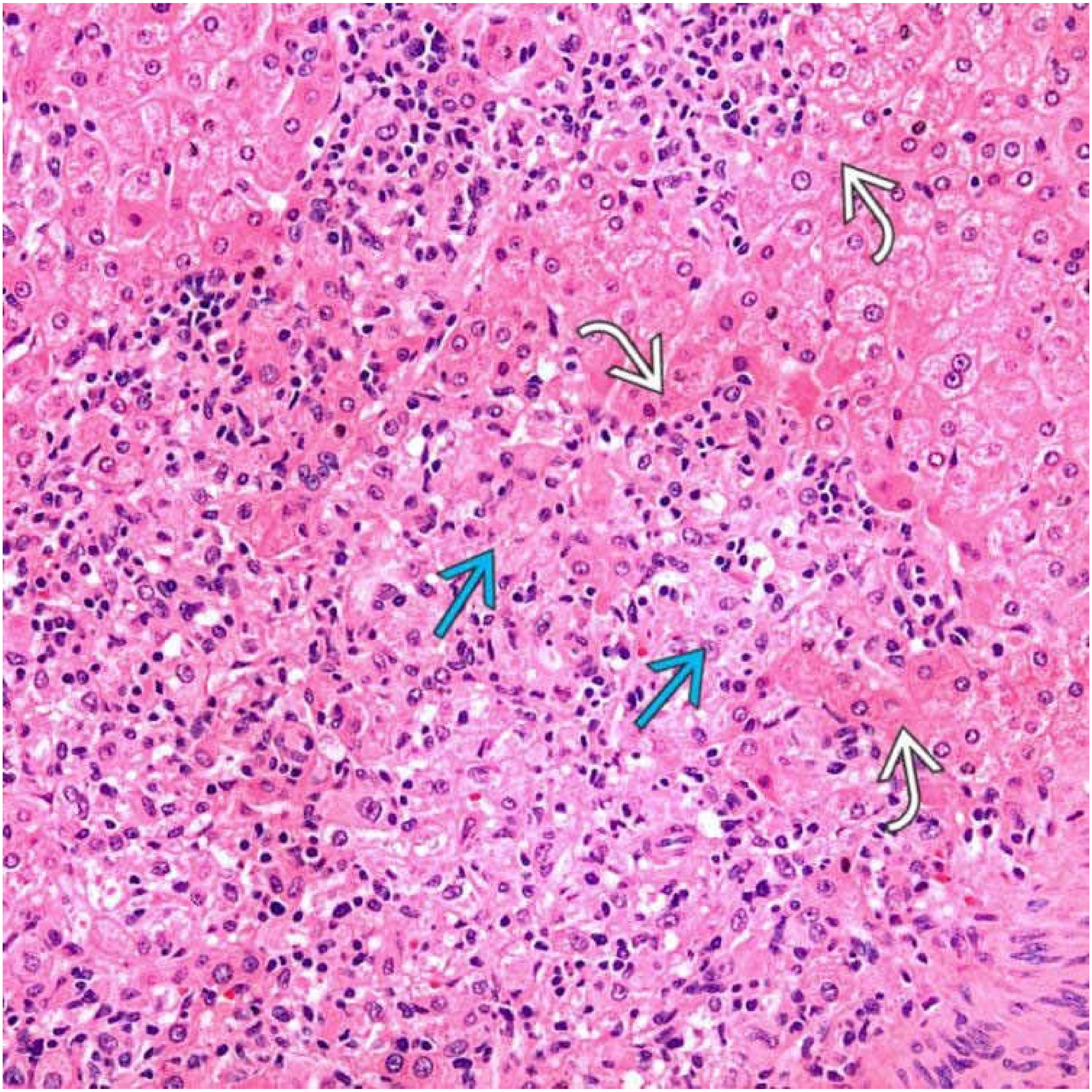
Gross photograph of a fixed specimen shows a heterogeneous, mottled, tan, yellow, and brown tumor with areas of hemorrhage and degeneration ➩. Note that the background liver is not cirrhotic.



Admixed Fat, Vessels, and Spindled Myoid Cells
Angiomyolipoma is composed of 3 admixed elements: Adipose tissue →, vessels ↷, and myoid cells ⇨, which in this case are plump and spindled.



Smooth Muscle Cells
The somewhat amphophilic and fibrillary cytoplasm of the smooth muscle cells of an angiomyolipoma contrasts with the more eosinophilic and granular hepatocyte cytoplasm .



Infiltrative Border
The infiltrative growth pattern of this angiomyolipoma → at the interface with background liver ↷ is not an indication of malignancy.

TERMINOLOGY

Abbreviations

- Angiomyolipoma (AML)

Synonyms

- PEComa

Definitions

- Rare, benign mesenchymal neoplasm composed of smooth muscle, adipose tissue, and vessels
  - Thought to arise from perivascular epithelioid cells (PEC); therefore, considered part of PEComa family of tumors

CLINICAL ISSUES

Epidemiology

- Incidence
  - Rare: Overall incidence unknown but only a few hundred cases reported
  - Some cases associated with tuberous sclerosis (6-10%), but less often than renal AML (20-40%)
    – More likely to be associated with tuberous sclerosis if multiple &/or associated with renal tumors
- Age
  - Adults 17-86 years (mean: 43.5-50 years)
- Sex
  - Marked female predominance

Presentation

- Most patients are asymptomatic and present incidentally
- Large tumors may cause symptoms related to mass effect or abdominal discomfort
- Tumor rupture is rare

Treatment

- Surgical approaches
  - Excision
    – When diagnosis cannot be established on biopsy
    – Symptomatic tumors
    – Large lesions at risk for rupturing
- Conservative approaches
  - If diagnosis can be confidently established, radiologic follow-up is recommended

Prognosis

- Benign behavior in nearly all cases
  - Tumor recurrence is uncommon
  - Metastasis extremely rare

IMAGING

Ultrasonographic Findings

- Most angiomyolipomas present as heterogeneous hyperechoic lesions, but can be hypoechoic

MR Findings

- MR is most specific imaging modality for detecting lipomatous component
- Most tumors are hypointense on T1WI and slightly hyperintense on T2WI

CT Findings

- Usually hypodense on precontrast CT

MACROSCOPIC

General Features

- Usually solitary, occasionally multiple
  - Well circumscribed
  - Either not encapsulated or only partially encapsulated
  - Cut surface is soft and yellow, tan, gray, or brown
  - May contain areas of hemorrhage and necrosis
- Background liver is typically noncirrhotic

Size

- 0.1-36 cm

MICROSCOPIC

Histologic Features

- Tumor consists of 3 elements in varying proportions
  - Adipose tissue
  - Blood vessels
  - Smooth muscle or “myoid” cells
- Smooth muscle (myoid) cells represent key diagnostic feature
  - Can be epithelioid, intermediate (ovoid or short spindle), or spindled
  - Epithelioid smooth muscle cells
    - Large, polygonal, or spheroid
    - May be clear, reticulated, vacuolated, or spider-web-like cytoplasm at periphery of cell
    - Cytoplasmic clearing is due to glycogen and occasionally small fat vacuoles in periphery of cells
    - Round to oval, eccentric nuclei that may be highly atypical
    - Mitoses rare or absent
    - Single eosinophilic nucleolus
    - May mimic hepatocytes
  - Spindled smooth muscle cells
    - Plump cells with round to oval pale nuclei
    - Rim of eosinophilic cytoplasm
- Variable features

- Intracytoplasmic hyaline globules
- Erythropoietic elements
- Hemorrhage/hemosiderin, peliosis
- Foamy macrophages, lymphocytic infiltrates
- Melanin
- Cholesterol clefts

- Tumor may show infiltration of surrounding liver sinusoids or even “invasion” into adjacent liver tissue
  - This finding is not indicative of biologic behavior
- No well-defined features predictive of malignant behavior
  - Large size (> 10 cm)
  - Coagulative necrosis
- Adipose component consists of mature adipose tissue
- Component blood vessels are abnormal
  - Tortuous vessels with thick walls

Cytologic Features

- Clusters of plump smooth muscle cells with arborizing traversing capillaries but admixed with adipocytes
- Smooth muscle cells show fibrillar cytoplasm, indistinct cytoplasmic borders, and spindle, elongate, or oval nuclei with nucleoli and occasional intranuclear inclusions

Variants

- Tumors composed predominantly of 3 key elements (adipose tissue, vessels, or myoid cells)
  - Myomatous, lipomatous, or angiomatous
- Tumors with predominantly or purely sinusoidal trabecular growth pattern
  - Frequently have little or no adipose tissue
  - May be misdiagnosed as hepatocellular carcinoma
- Oncocytic AML
  - Relatively homogeneous cytologic features
  - Little or no adipose tissue
  - Prominent degenerative-type cytologic atypia
- Histologic variants have no bearing on prognosis, specific symptoms, or gross tumor characteristics

ANCILLARY TESTS

Histochemistry

- PAS-diastase
  - Reactivity: Positive
  - Staining pattern: Hyaline globules
- Iron
  - Reactivity: Positive

- Staining pattern: Stains hemosiderin in some tumors

- Fontana-Masson
  - Reactivity: Positive
  - Staining pattern: Stains melanin pigment in some tumors

Immunohistochemistry

- Smooth muscle (myoid) cells stain with antibodies to HMB-45, smooth muscle actin
  - Other melanoma markers, such as Melan-A, tyrosinase, MITF, often positive in myoid cells
  - Epithelioid smooth muscle markers in smooth muscle cells stain most intensely with HMB-45 and are less likely to stain with usual melanocyte markers
  - Spindle smooth muscle cells stain most intensely with actin-sm, myosin, desmin, and vimentin, and less intensely with HMB-45
  - Occasionally S100 and NSE positive
  - Hep-Par1 and arginase negative in myoid cells
    – Useful to distinguish epithelioid myoid cells from benign or malignant hepatocytes
- Myoid cells are keratin negative
- Mature adipocytes frequently stain with antibodies to S100 and vessels stain with CD34 and other vascular markers

Flow Cytometry

- Diploid DNA pattern, favoring benign nature

Electron Microscopy

- Cytoplasmic-bound granules consistent with premelanosomes and intracytoplasmic filaments that aggregate to produce dense bodies

DIFFERENTIAL DIAGNOSIS

Hepatocellular Neoplasm

- Hepatocellular adenoma or hepatocellular carcinoma
- May see steatosis but no adipocytes
- Stains with keratins and hepatocyte markers (Hep-Par1, arginase)
- HMB-45 and actin negative

Metastatic Malignant Tumor

- Sarcoma or carcinoma
- Lacks adipose tissue component
- Immunohistochemistry distinguishes AML from other neoplasms

Malignant Melanoma

- Absence of adipose tissue component
- Immunohistochemistry shows staining for S100 in spindle or epithelioid cells

Gastrointestinal Stromal Tumor

- Absence of adipose tissue
- Positive staining with CD117, DOG1, and CD34
- HMB-45 negative

Smooth Muscle Tumor

- Leiomyoma or leiomyosarcoma
- Lacks adipose tissue
- HMB-45 negative

Lipoma, Focal Fatty Change, or Myelolipoma

- Absence of spindle or epithelioid cell component that stains with HMB-45

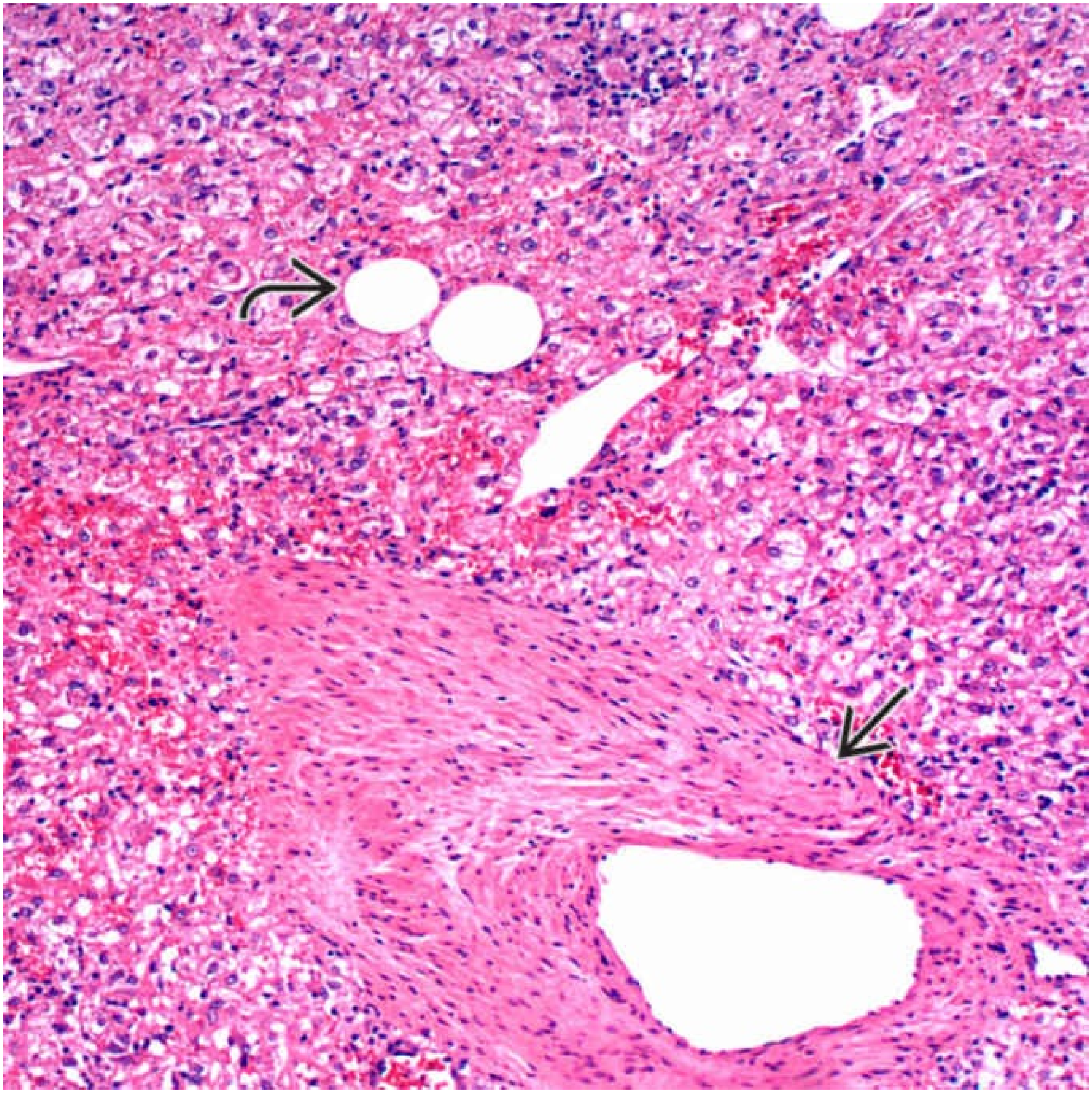
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

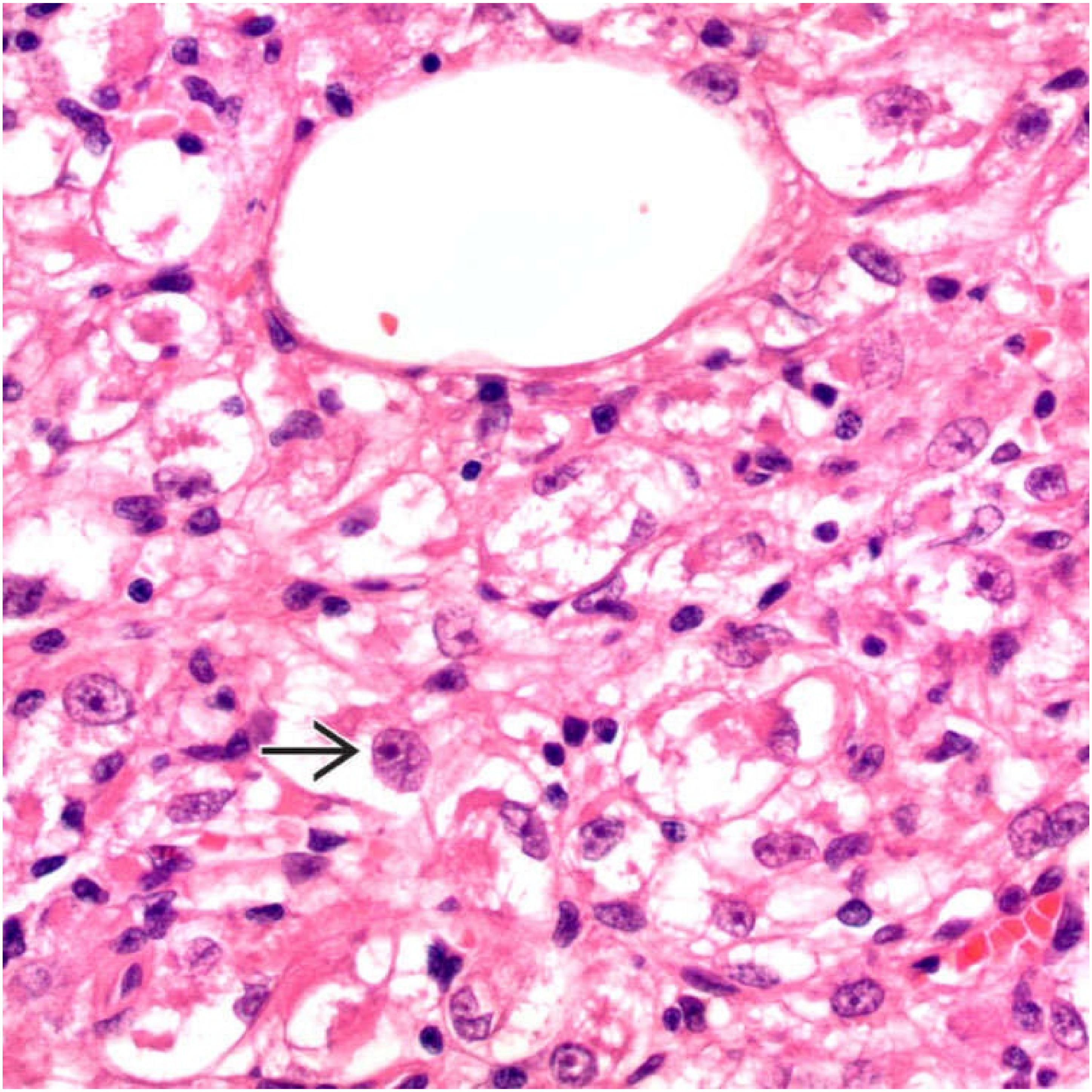
- Fat component may be noted on radiologic studies

Pathologic Interpretation Pearls

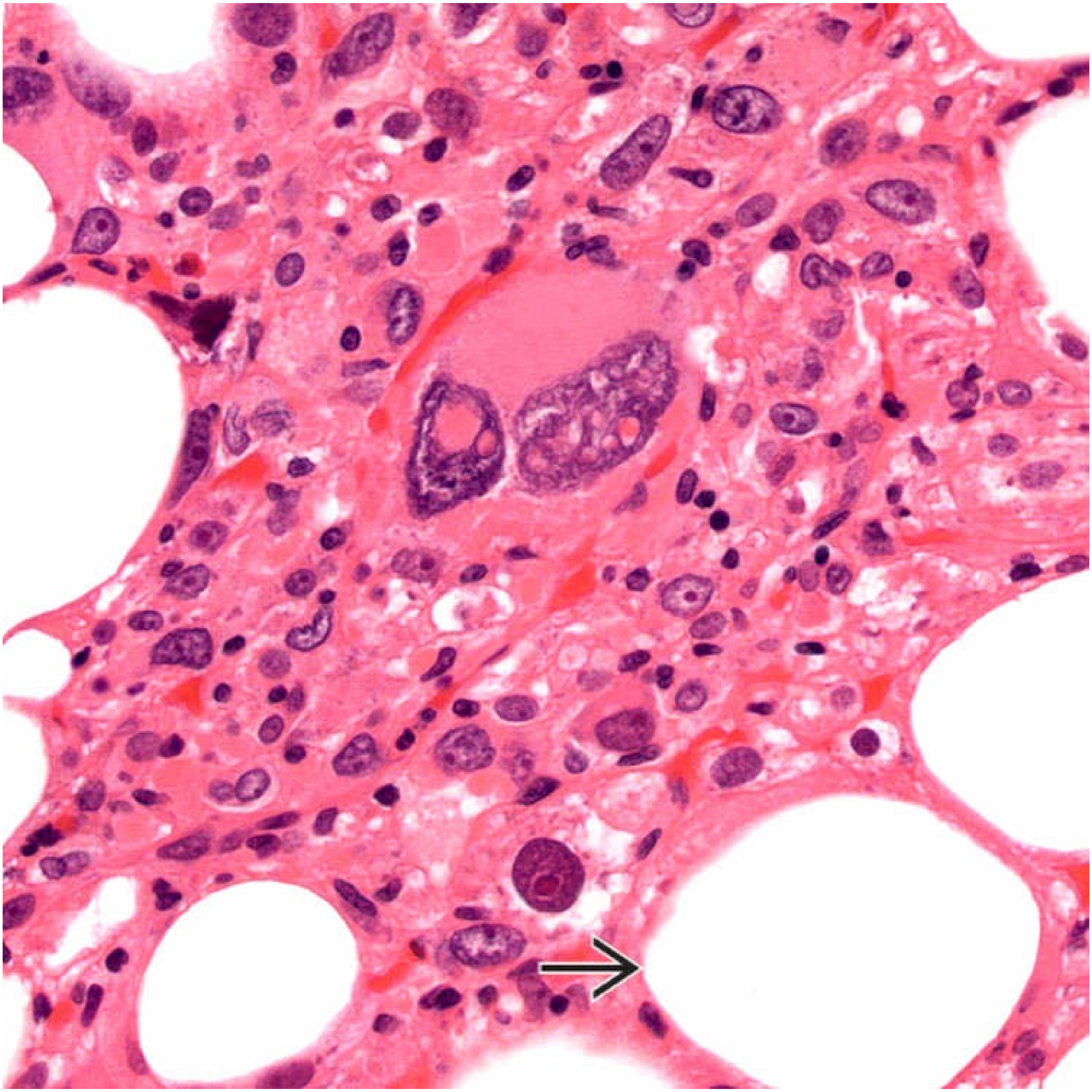
- Heterogeneous tumor that contains mixture of plump eosinophilic cells and fat should raise suspicion for angiomyolipoma
- HMB45 immunohistochemistry advisable for unusual presumed carcinomas or sarcomas of liver



Abnormal Vessels
This tumor is composed largely of plump spindle and epithelioid cells, with scant adipose tissue ↱ and abnormal thickened vessels → .

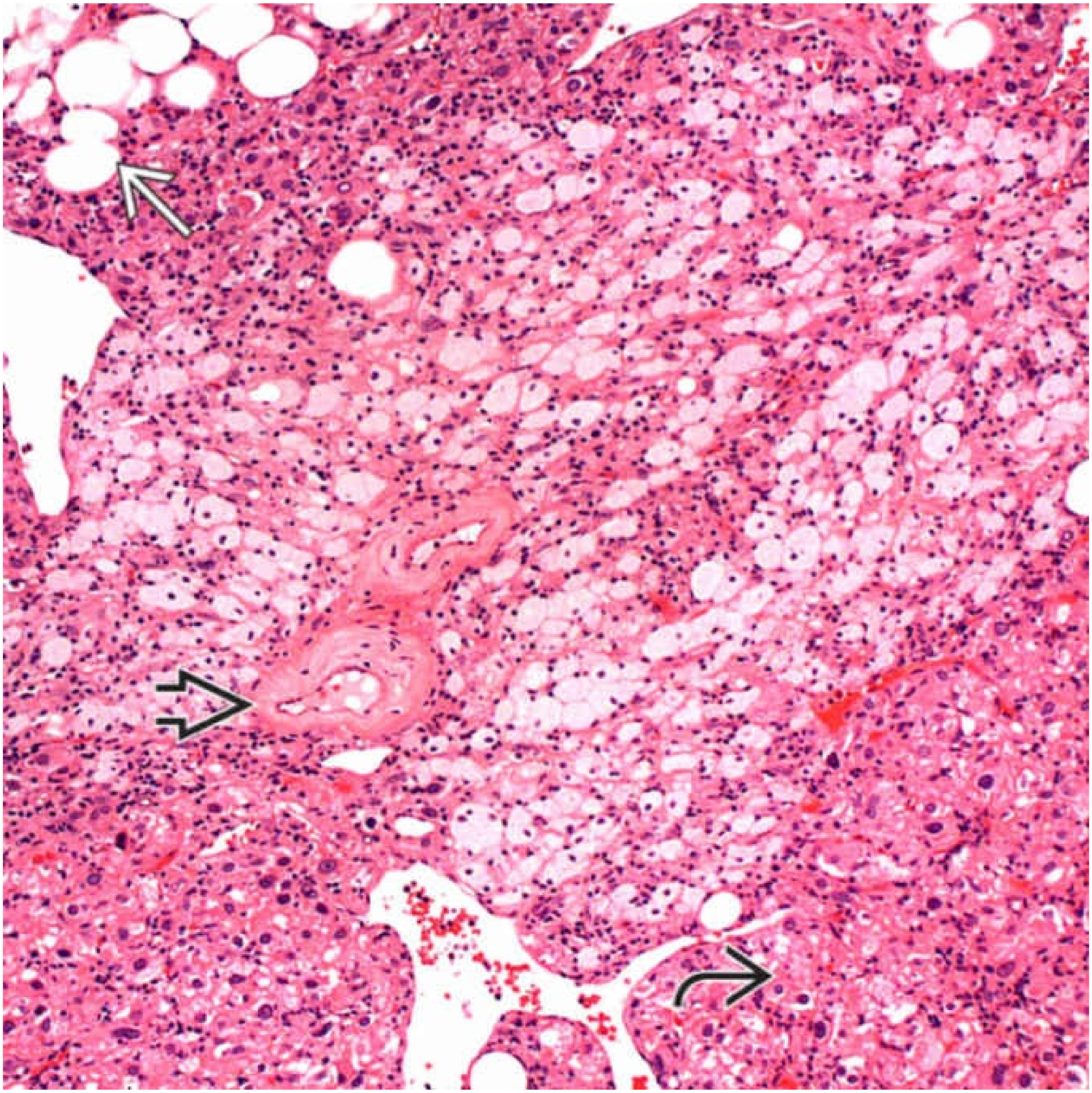


Epithelioid Smooth Muscle Cells
Epithelioid smooth muscle cells in angiomyolipoma have rarefied cytoplasm that resembles spider webs. Note the enlarged oval nuclei and distinct nucleoli → .



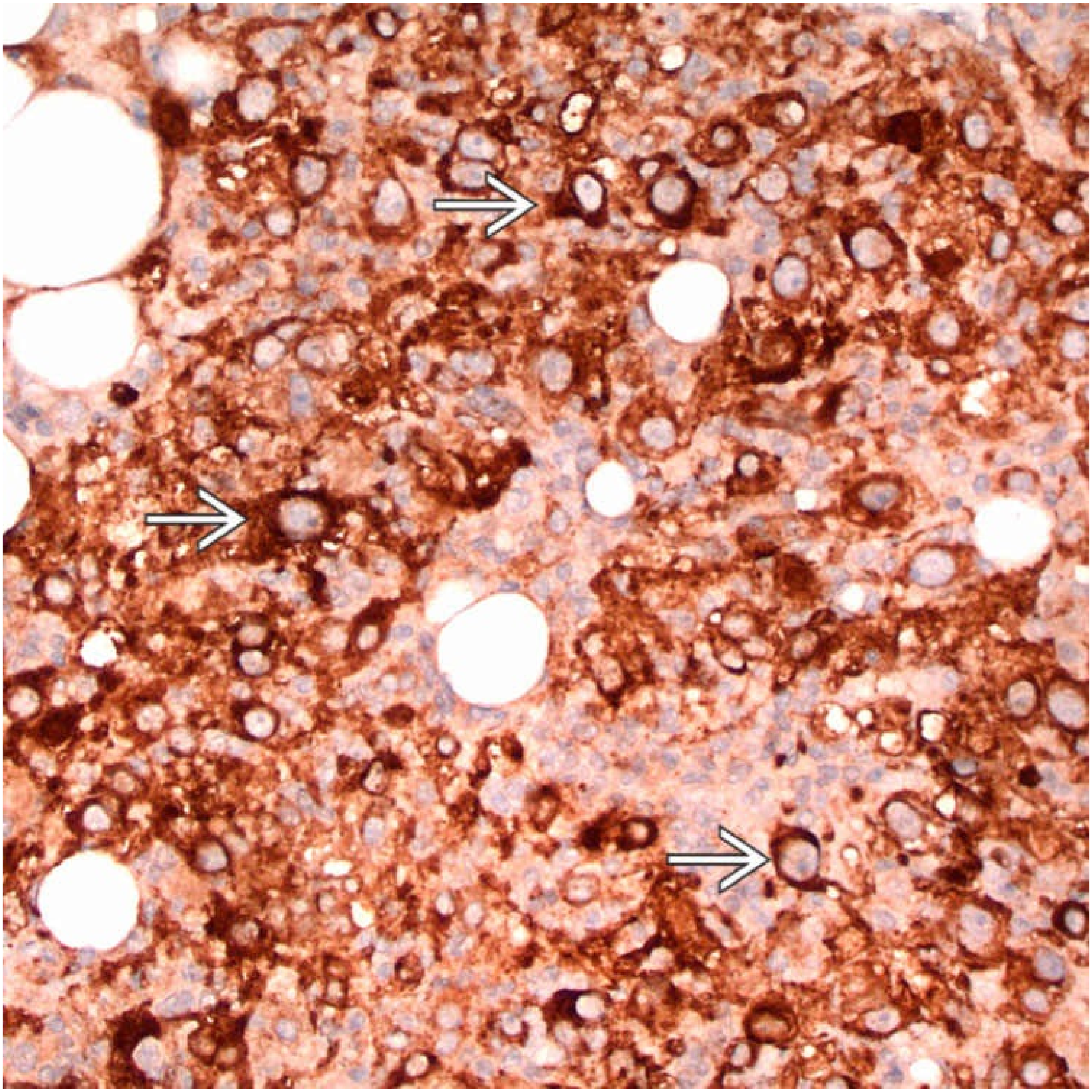
Smooth Muscle Cells With Atypia

These highly atypical epithelioid cells with markedly enlarged nuclei, binucleation, intranuclear inclusions, and coarse chromatin are closely admixed with adipocytes →. Mitoses are absent.

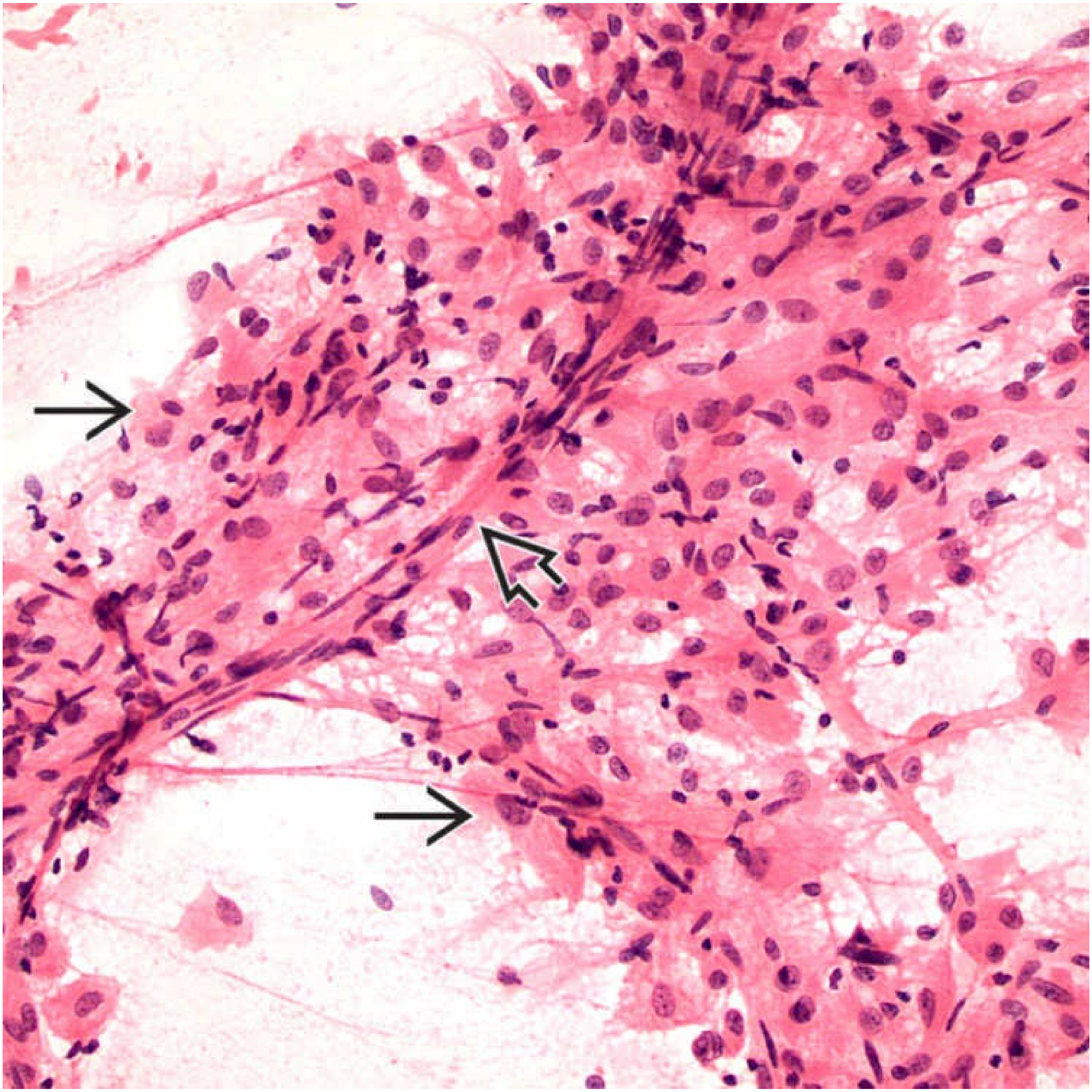


Foamy Macrophages

Aggregates of foamy macrophages and lymphocytes are present within this angiomyolipoma. The smooth muscle cells, adipocytes, and abnormal vessels typical of angiomyolipoma are present as well.



HMB-45 Staining
HMB-45 immunostain shows strong positive staining ⇒ in the epithelioid smooth muscle cells. This is a characteristic feature.



Cytologic Features
An intraoperative tumor smear shows loosely cohesive epithelioid smooth muscle cells → with oval nuclei adherent to traversing vessels ⇨ .

SELECTED REFERENCES

1. Yang, X, et al. Hepatic angiomyolipoma: clinical, imaging and pathological features in 178 cases. *Med Oncol*. 2013; 30(1):416.
2. Li, T, et al. Hepatic angiomyolipoma: a retrospective study of 25 cases. *Surg Today*. 2008; 38(6):529–535.
3. Nguyen, TT, et al. Malignant hepatic angiomyolipoma: report of a case and review of literature. *Am J Surg Pathol*. 2008; 32(5):793–798.
4. Petrolla, AA, et al. Hepatic angiomyolipoma. *Arch Pathol Lab Med*. 2008; 132(10):1679–1682.

5. Hornick, JL, et al. PEComa: what do we know so far? *Histopathology*. 2006; 48(1):75–82.
6. Xu, AM, et al. Pathological and molecular analysis of sporadic hepatic angiomyolipoma. *Hum Pathol*. 2006; 37(6):735–741.
7. Lin, KJ, et al. Hepatic angiomyolipoma: report of two cases with emphasis on smear cytomorphology and the use of cell block with immunohistochemical stains. *Diagn Cytopathol*. 2004; 31(4):263–266.
8. Makhlouf, HR, et al. Expression of KIT (CD117) in angiomyolipoma. *Am J Surg Pathol*. 2002; 26(4):493–497.
9. Ji, Y, et al. Hepatic angiomyolipoma: a clinicopathologic study of 10 cases. *Chin Med J (Engl)*. 2001; 114(3):280–285.
10. Tsui, WM, et al. Hepatic angiomyolipoma: a clinicopathologic study of 30 cases and delineation of unusual morphologic variants. *Am J Surg Pathol*. 1999; 23(1):34–48.
11. Nonomura, A, et al. Angiomyolipoma predominantly composed of smooth muscle cells: problems in histological diagnosis. *Histopathology*. 1998; 33(1):20–27.
12. Sawai, H, et al. Angiomyolipoma of the liver: case report and collective review of cases diagnosed from fine needle aspiration biopsy specimens. *J Hepatobiliary Pancreat Surg*. 1998; 5(3):333–338.
13. Nonomura, A, et al. Immunohistochemical study of hepatic angiomyolipoma. *Pathol Int*. 1996; 46(1):24–32.

Epithelioid Hemangioendothelioma

KEY FACTS

Etiology/Pathogenesis

- t(1;3) translocation resulting in WWTR1-CAMTA1 fusion protein
- t(1;3) resulting in WWTR1-CAMTA1 fusion protein in > 80%
- YAP1-TFE3 fusion in a small subset

Clinical Issues

- Rare, low-grade malignant vascular neoplasm
- Prognosis better than angiosarcoma

Macroscopic

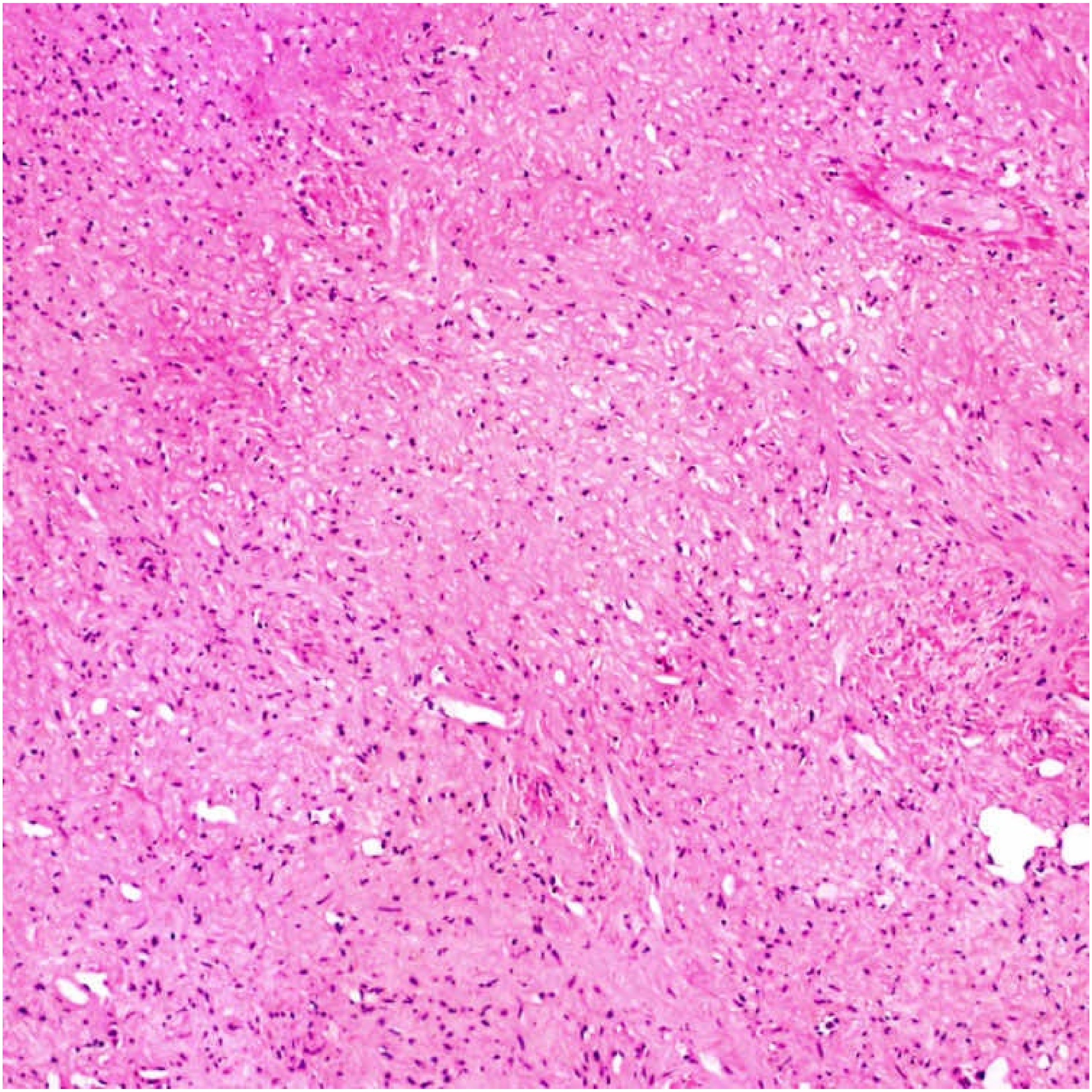
- Firm, white to yellow with ill-defined borders

Microscopic

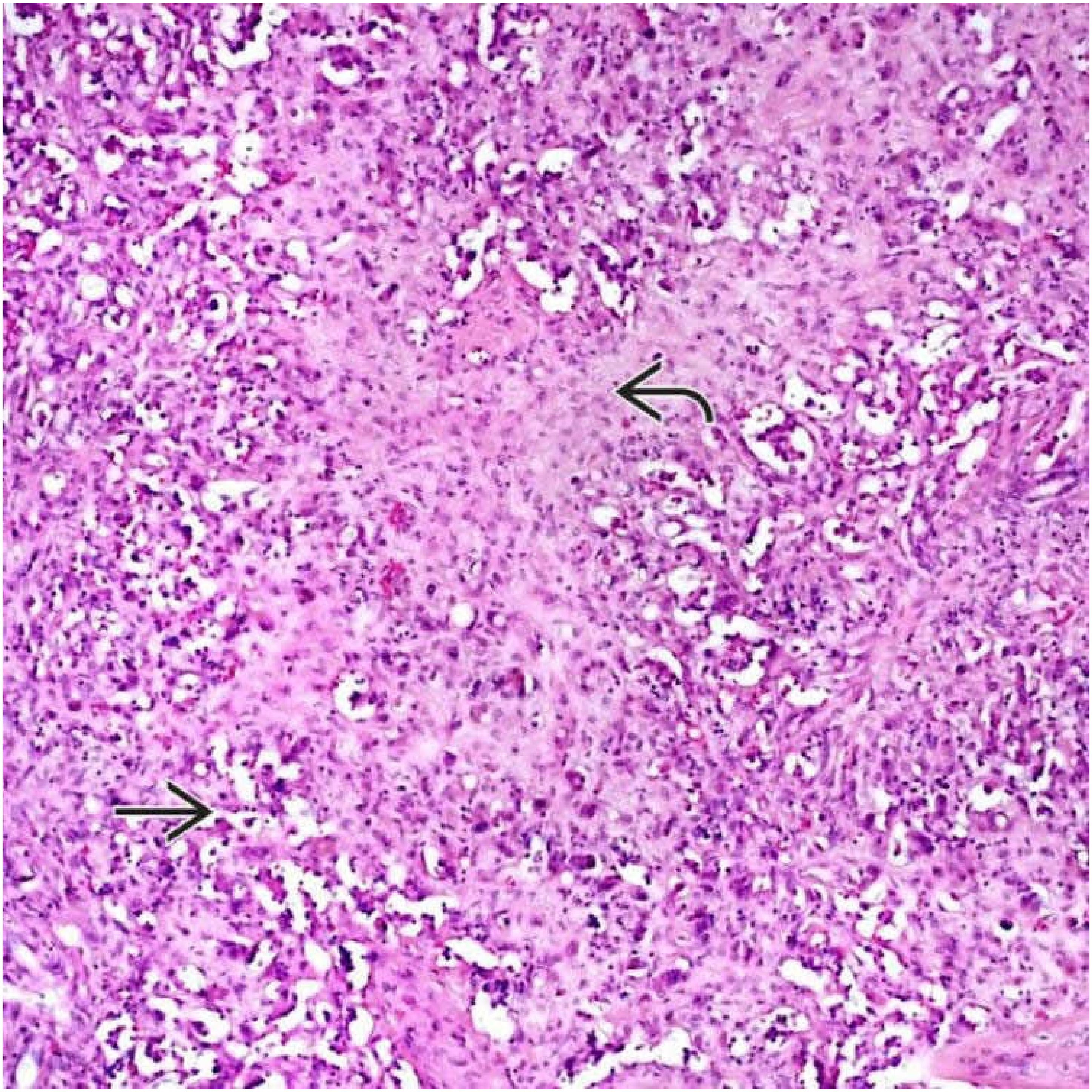
- Central portion is fibrotic and paucicellular
  - Dendritic or epithelioid tumor cells, often with intracytoplasmic vacuoles, in fibrous stroma
  - Tumor cells express vascular markers like CD31, ERG, and FLI-1
  - Tumors with WWTR1-CAMTA1 fusion
  - Nuclear staining with CAMTA1 immunohistochemistry
- Tumors with YAP1-TFE3
  - Well-formed vascular channels, tumor cells with voluminous eosinophilic cytoplasm
  - Nuclear staining with TFE3 immunohistochemistry

Top Differential Diagnoses

- Dense myxoid stroma and intracytoplasmic vacuoles can mimic adenocarcinoma
- Greater nuclear atypia, mitotic activity, and destructive growth pattern distinguish angiosarcoma from epithelioid hemangioendothelioma

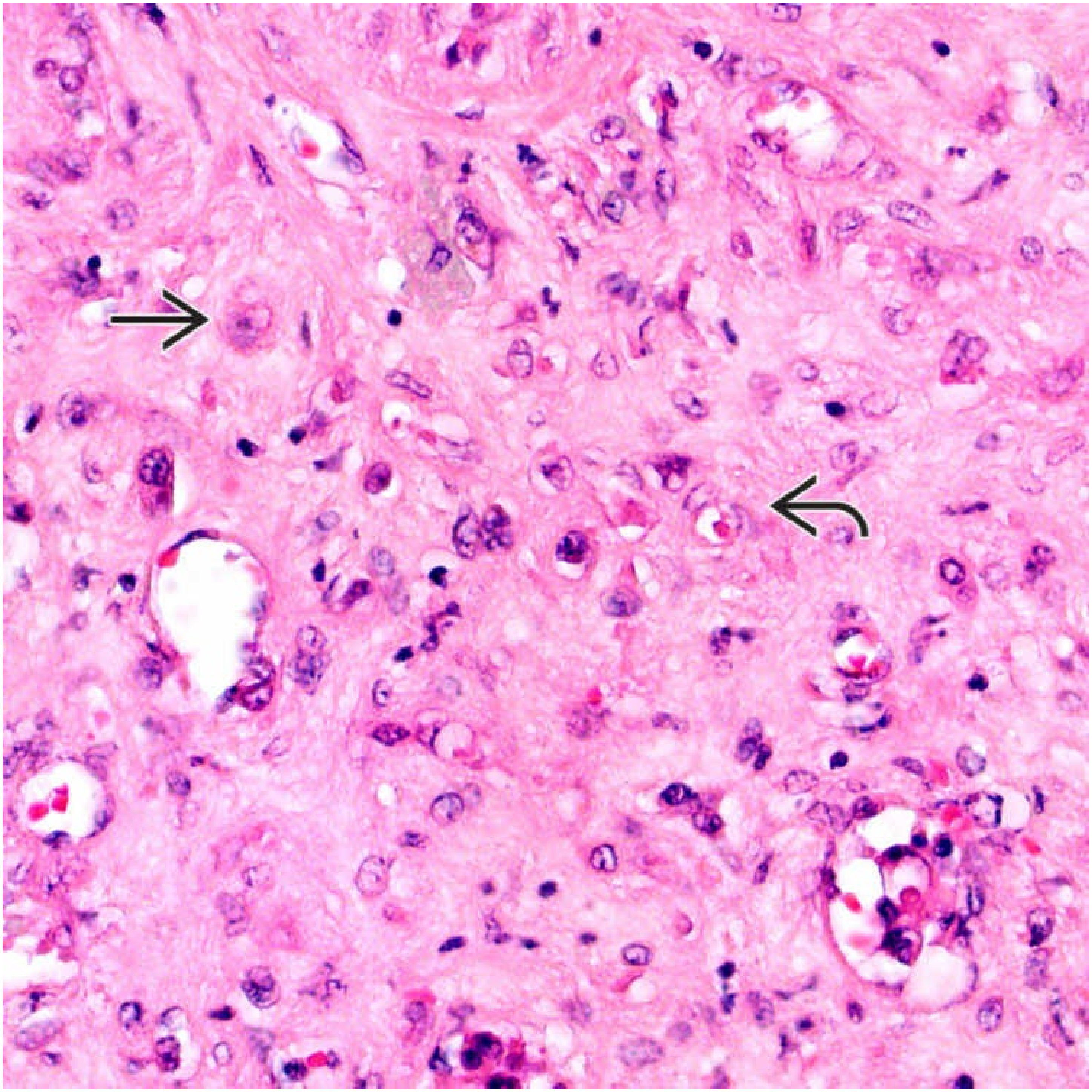


Central Hypocellular Zone
Central portion is typically hypocellular with loosely arranged spindle cells in a fibromyxoid or sclerotic stroma. The findings can simulate a scar or sclerosed hemangioma.

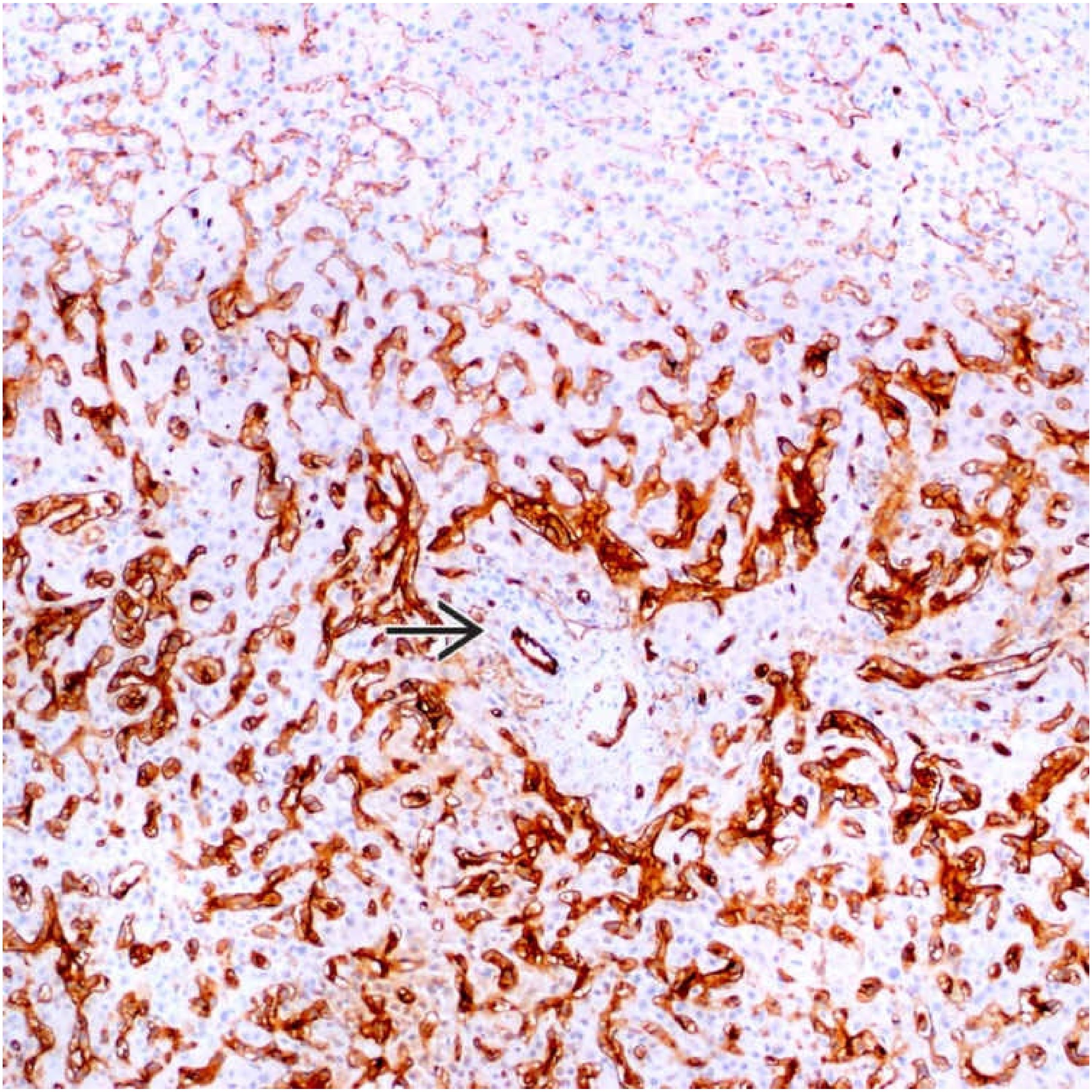


Poorly Formed Vascular Lumina

Poorly formed vascular lumina → and infiltrating tumor cells in a fibromyxoid stroma ↷ can mimic cholangiocarcinoma.



Intracytoplasmic Lumina
Cellular area with epithelioid tumor cells → in a fibromyxoid stroma demonstrates mild nuclear atypia with no mitoses. Vascular differentiation is seen in the form of intracytoplasmic lumina with red blood cells ↷ .



CD31 Staining
CD31 is strongly expressed in tumor cells, highlighting the characteristic infiltrative pattern with entrapment of portal tracts → and extension along the sinusoids in adjacent liver.

TERMINOLOGY

Abbreviations

• Epithelioid hemangioendothelioma (EHE)

Definitions

• Uncommon, considered low-grade malignancy

ETIOLOGY/PATHOGENESIS

Molecular Changes

- t(1;3) resulting in WWTR1-CAMTA1 fusion protein in > 80%
- YAP1-TFE3 fusion in small subset

CLINICAL ISSUES

Presentation

- Primarily affects adults (30-40 years)
  - Rare in children
- Slightly more common in women
- Upper abdominal mass or discomfort and elevated alkaline phosphatase may be present
  - Often discovered as incidental finding

Treatment

- Primary treatment is hepatic resection
  - Liver transplantation in unresectable cases
  - Extrahepatic spread not contraindication for transplant
- Radiotherapy and chemotherapy generally ineffective

Prognosis

- Natural history is extremely variable
  - Long survival despite no treatment or incomplete resection in some cases
  - Adverse outcome in others despite adequate resection and adjuvant therapy
- Prognosis better than angiosarcoma, even with incomplete excision or extrahepatic metastases

IMAGING

General Features

- Multinodular EHE can mimic metastatic disease
- Hypoechoic nodules on ultrasound, hypodense on CT scan
- MR: Low signal intensity on T1-weighted images, high signal intensity on T2-weighted images
- Peripheral enhancement and hypodense rim with contrast

MACROSCOPIC

General Features

- Firm, white to yellow with ill-defined borders
  - Focal calcification can cause gritty consistency

- Can be multifocal with involvement of both lobes
- 2 different types, depending on distribution in liver
  - Nodular: Early stage of disease; observed in 10%
  - Diffuse: Advanced stage, due to coalescence of multiple lesions

MICROSCOPIC

Histologic Features

- Infiltrates preexisting structures, leaves portal zones and central veins intact
  - Periphery has higher cellularity
  - Center of tumor is often fibrotic and paucicellular
- Myxoid to fibrous stroma
  - Calcification may be present in dense areas of stroma
- Intravascular small papillary projections or tufts can occur
- Tumor cells are dendritic or epithelioid
  - Dendritic: Irregular, elongated, or stellate with branching processes
  - Epithelioid: Round with more abundant cytoplasm
  - Cytoplasmic vacuole may represent intracellular lumina and may have erythrocytes
  - Nuclear atypia and mitoses typically not prominent
- Scattered inflammatory cells such as lymphocytes and neutrophils often present
- Residual hepatocytes or bile ducts can be present within tumor
- Invasion of portal and central veins mimics vascular thrombosis
- “Malignant” EHE
  - Rare tumors with higher nuclear grade, increased mitosis, and solid growth
  - More aggressive than conventional EHE
- Immunohistochemical features
  - Vascular markers like CD31, CD34, &/or FVIIIRAg are usually positive
  - ERG and FLI-1, endothelial transcription factors of ETS family, are expressed in nuclei of tumor cells
  - Podoplanin (recognized by antibody D2-40), a lymphatic endothelial marker, is expressed in 70% of EHE
    - D2-40 is not expressed in angiosarcoma although experience with this is limited
  - Tumors with WWTR1-CAMTA1 fusion
    - Nuclear staining with CAMTA1 immunohistochemistry
    - High specificity for diagnosis
  - Tumors with YAP1-TFE3
    - Areas with well-formed vascular channels
    - Tumor cells with voluminous eosinophilic cytoplasm
    - Nuclear staining with TFE3 immunohistochemistry

DIFFERENTIAL DIAGNOSIS

Adenocarcinoma (Including Cholangiocarcinoma)

- Intracytoplasmic lumina and dense sclerotic stroma in EHE can be mistaken for adenocarcinoma
- Focal keratin positivity in EHE due to entrapped hepatocytes, bile ducts, and tumor cells can mimic carcinoma
- Favor EHE: Young age, multifocal involvement, pattern of tumor infiltration at periphery calcification
- Endothelial markers in tumor cells confirm EHE

Angiosarcoma

- Tend to be large and hemorrhagic
- Greater nuclear atypia, mitoses, and destructive growth pattern
- Both express endothelial markers

SELECTED REFERENCES

1. Doyle, LA, et al. Nuclear expression of CAMTA1 distinguishes epithelioid hemangioendothelioma from histologic mimics. *Am J Surg Pathol*. 2016; 40(1):94–102.
2. Flucke, U, et al. Epithelioid hemangioendothelioma: clinicopathologic, immunhistochemical, and molecular genetic analysis of 39 cases. *Diagn Pathol*. 2014; 9:131.
3. Errani, C, et al. A novel WWTR1-CAMTA1 gene fusion is a consistent abnormality in epithelioid hemangioendothelioma of different anatomic sites. *Genes Chromosomes Cancer*. 2011; 50(8):644–653.
5. Weinreb, I, et al. CD10 is expressed in most epithelioid hemangioendotheliomas: a potential diagnostic pitfall. *Arch Pathol Lab Med*. 2009; 133(12):1965–1968.
7. Mehrabi, A, et al. Primary malignant hepatic epithelioid hemangioendothelioma: a comprehensive review of the literature with emphasis on the surgical therapy. *Cancer*. 2006; 107(9):2108–2121.
8. Uchimura, K, et al. Hepatic epithelioid hemangioendothelioma. *J Clin Gastroenterol*. 2001; 32(5):431–434.

4. Lin, J, et al. CT and MRI diagnosis of hepatic epithelioid hemangioendothelioma. *Hepatobiliary Pancreat Dis Int*. 2010; 9(2):154–158.
6. Fujii, T, et al. Podoplanin is a useful diagnostic marker for epithelioid hemangioendothelioma of the liver. *Mod Pathol*. 2008; 21(2):125–130.

Infantile Hemangioma

KEY FACTS

Terminology

- Originally described as infantile hemangioendothelioma type 1

Clinical Issues

- Most common hepatic neoplasm in 1st year of life
- Most present before age of 6 months

Macroscopic

- Solitary or multifocal, nonencapsulated

Microscopic

- Vascular proliferation resembling small capillaries
  - Slightly dilated and irregular in shape
  - Lined by single layer of bland endothelial cells
- Secondary involutional changes in central portion
- Peripheral cellular areas show proliferation of vascular channels in loose fibrous stroma

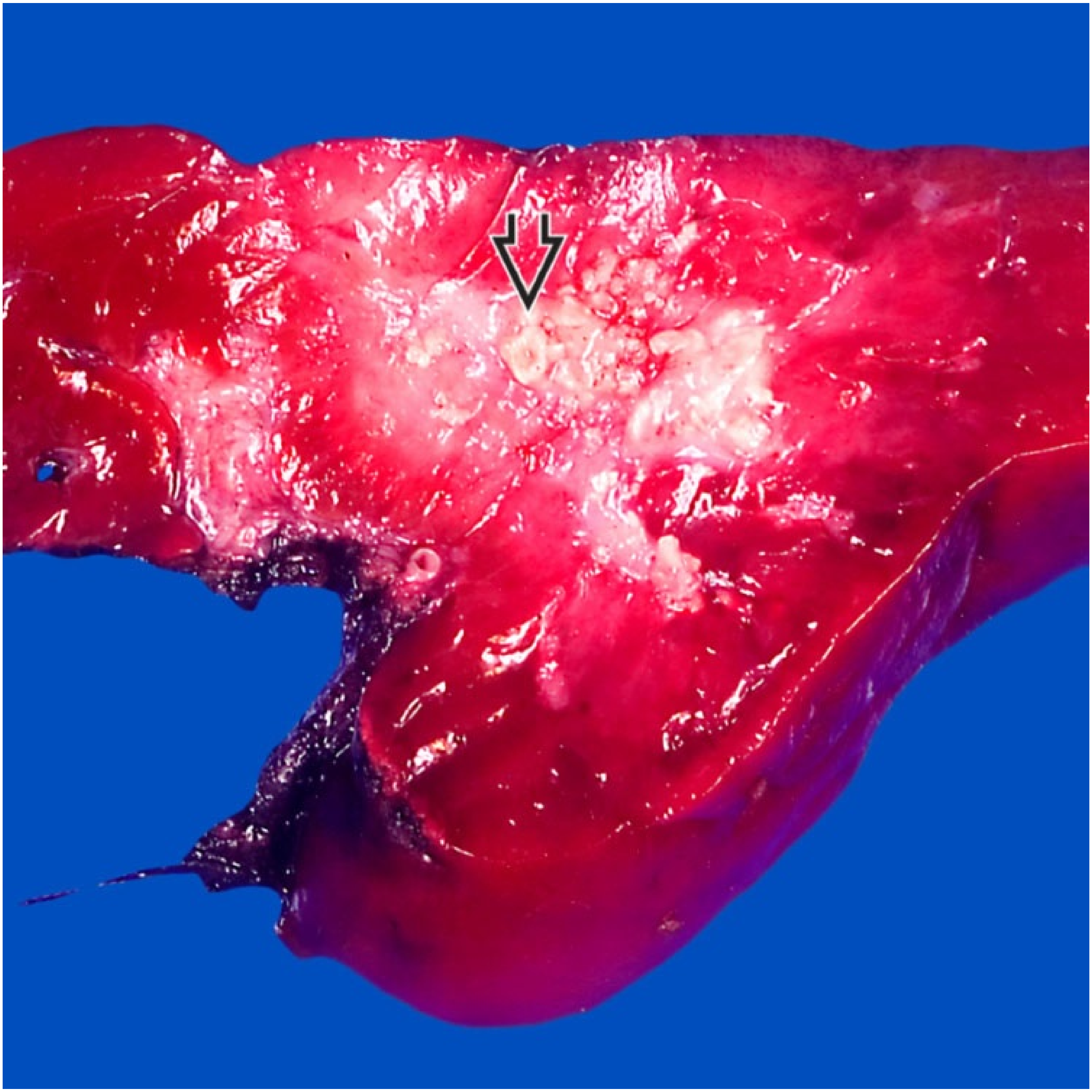
Ancillary Tests

- Positive for vascular markers: Factor VIII, CD31, CD34, FLI-1
- GLUT-1 is often positive, while most vascular malformations are negative

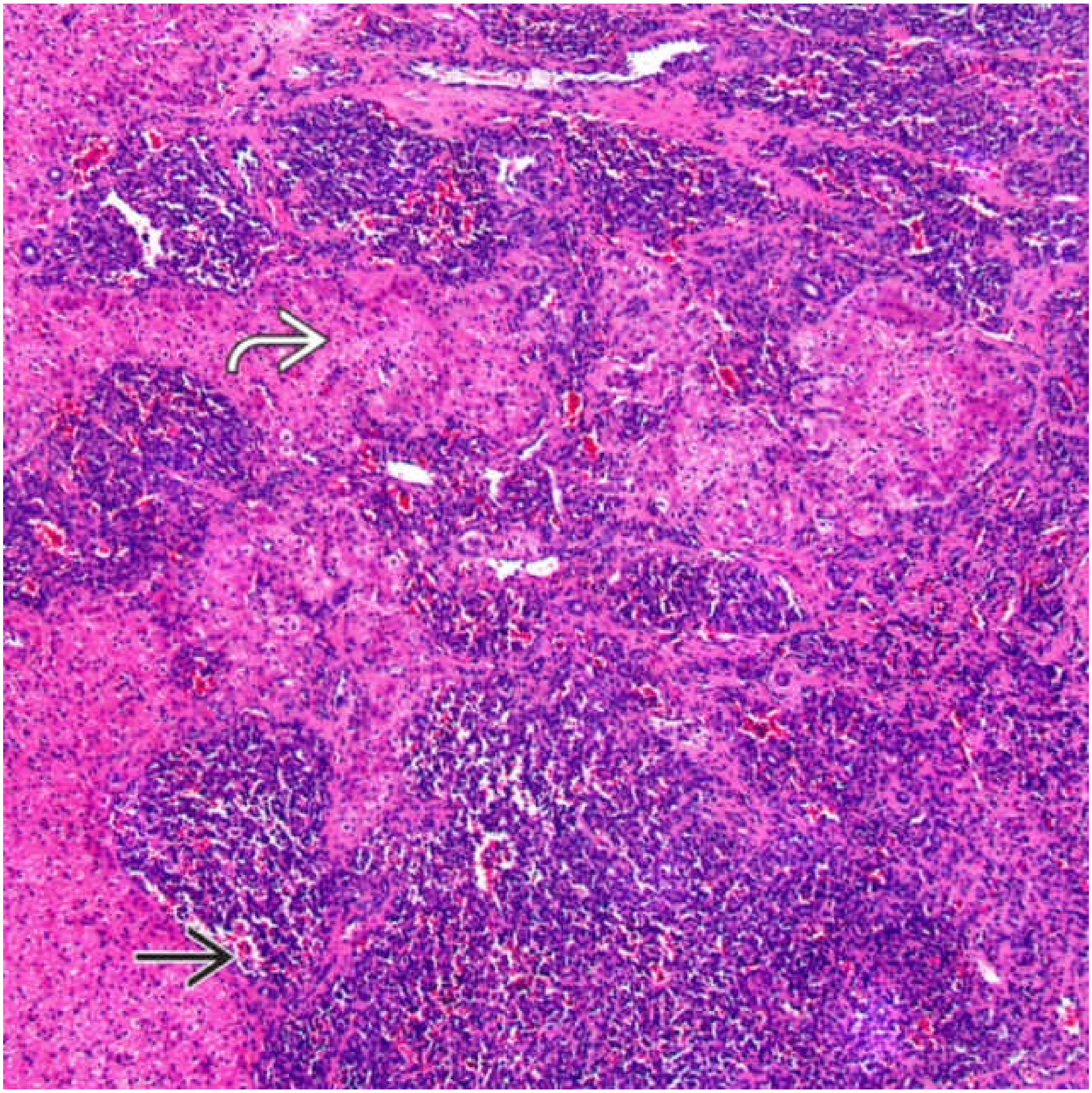
Top Differential Diagnoses

- Angiosarcoma
  - Previously termed infantile hemangioendothelioma type 2
  - Key distinguishing feature is nuclear atypia of endothelial cells

• Cavernous hemangioma
• Lymphangioma
• Mesenchymal hamartoma
• Vascular malformation

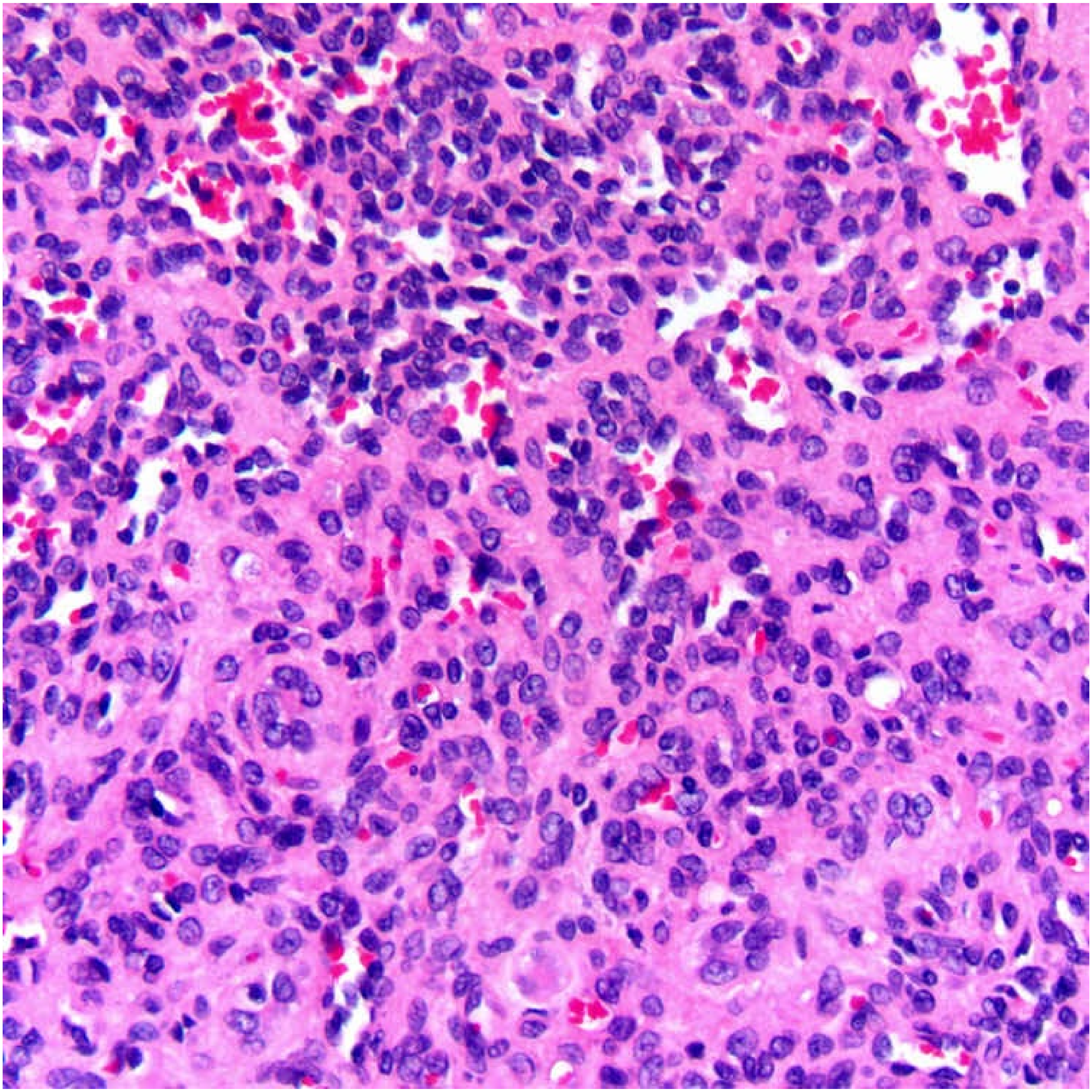


Poorly Circumscribed Mass
This partial hepatectomy specimen shows a poorly circumscribed, white-tan mass ➩ with central calcification. Infantile hemangioma may present as a solitary or multifocal lesion.



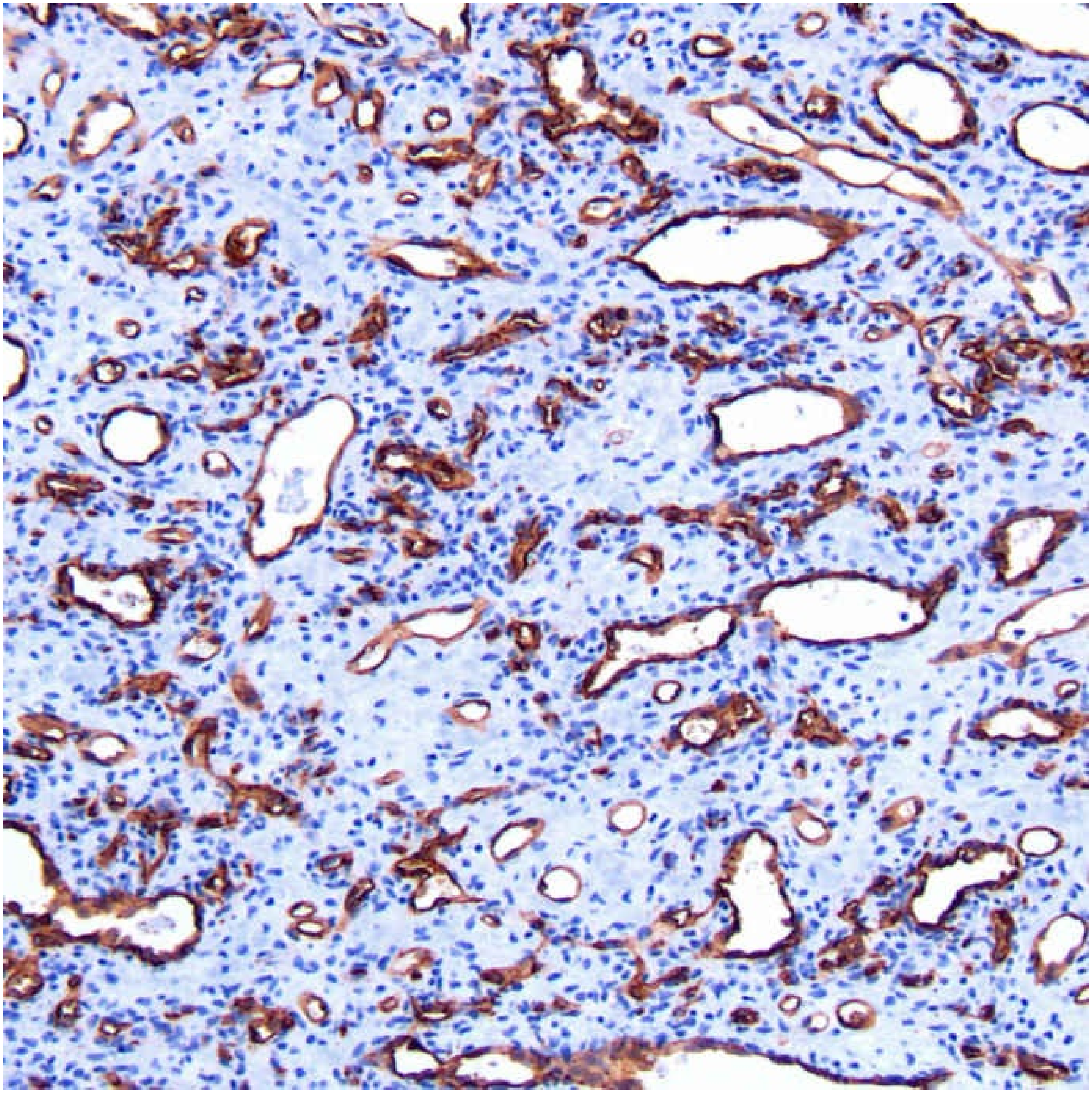
Cellular Peripheral Portion

The peripheral, highly cellular portion of an infantile hemangioma shows an irregular interface with the hepatic parenchyma and is partially entrapping it .



Closely Packed Vessels

A closer view of the cellular peripheral portion of the tumor shows densely packed vascular channels lined by a single layer of plump endothelial cells without significant cytologic atypia.



CD34 Immunohistochemistry
The endothelial cells lining the irregular, variably dilated, capillary-like vascular channels are immunoreactive for the endothelial marker CD34.

TERMINOLOGY

Synonyms

- Originally described by Dehner and Ishak as infantile hemangioendothelioma type 1

Definitions

- Hepatic vascular neoplasm
  - Most common hepatic neoplasm during 1st year of life
  - Accounts for 15% of primary liver tumors in pediatric population

CLINICAL ISSUES

Epidemiology

- Age
  - Most present before age of 6 months
  - Rare in adults
- Sex
  - Female predominance

Presentation

- Hepatomegaly, abdominal enlargement, palpable mass
  - Small tumors may be asymptomatic
- Frequently have cutaneous hemangiomas, hypothyroidism
- Complications
  - High-output cardiac failure due to shunting through tumor
  - Kasabach-Merritt syndrome
    - Thrombocytopenia, hypofibrinogenemia

Natural History

- Spontaneous regression (5-10%)
- Malignant transformation has been reported

Treatment

- Intravenous steroids, beta-blockers, chemotherapy
- Hepatic artery ligation, embolization of feeding vessels
- Surgical resection
- Orthotopic liver transplantation

Prognosis

- Survival rate of 70% with treatment
- Diffuse disease and cardiac failure are adverse prognostic factors

MACROSCOPIC

General Features

- Solitary or multifocal, nonencapsulated
- Size ranges from 0.3-13 cm

MICROSCOPIC

Histologic Features

- Peripheral cellular areas show proliferation of vascular channels in loose fibrous stroma
  - Small, capillary-like, and thin walled
  - Slightly dilated and irregular
  - Some ectatic (cavernous) vessels
- Entrapped hepatocytes and bile ducts near periphery
- Secondary involutional changes in central portion
  - Myxoid change, necrosis, fibrosis, thrombosis, calcification

Cytologic Features

- Single layer of bland endothelial cells
  - Elongated plump cells with scant cytoplasm
  - Round to oval nuclei with finely granular nuclear chromatin
  - Mitoses often present in peripheral cellular area

ANCILLARY TESTS

Immunohistochemistry

- Positive for vascular markers: Factor VIII, CD31, CD34, FLI-1
  - Endothelial cells are surrounded by smooth muscle actin immunoreactivity
  - Negative for desmin
- GLUT-1 is often positive, while most vascular malformations are negative

DIFFERENTIAL DIAGNOSIS

Angiosarcoma

- Previously termed infantile hemangioendothelioma type 2
  - Poorly formed, irregular, branching, and budding vascular spaces
  - Lined by stratified and atypical endothelial cells
    - Pleomorphic, large, and hyperchromatic nuclei
- Peripheral region of sinusoidal growth pattern
  - Dilated sinusoids lined by enlarged atypical cells
- Kaposiform spindle cell areas
- Absence of bile ducts within tumor

Cavernous Hemangioma

- Large, dilated, thin-walled, blood-filled spaces
  - Lined by flattened endothelium

Lymphangioma

- Large vascular spaces with attenuated endothelium
  - Spaces filled with proteinaceous fluid
  - Small lymphoid aggregates in stroma
- Immunoreactive for D2-40

Mesenchymal Hamartoma

- Overlapping age and clinical presentation
- Contains mixture of epithelial and stromal components
- Cystic spaces not lined by endothelial cells
- Vessels are thick walled with round lumina

Vascular Malformation

- Often presents early in infancy
- Large, thick-walled vessels typical of arteriovenous malformation
- Can be indistinguishable from infantile hemangioma in some areas
- GLUT-1 tends to be negative

SELECTED REFERENCES

1. Yeh, I, et al. Diffuse infantile hepatic hemangiomas: a report of four cases successfully managed with medical therapy. *Pediatr Dermatol*. 2011; 28(3):267–275.
2. Mo, JQ, et al. GLUT1 endothelial reactivity distinguishes hepatic infantile hemangioma from congenital hepatic vascular malformation with associated capillary proliferation. *Hum Pathol*. 2004; 35(2):200–209.
3. Awan, S, et al. Angiosarcoma of the liver in children. *J Pediatr Surg*. 1996; 31(12):1729–1732.
4. Selby, DM, et al. Infantile hemangioendothelioma of the liver. *Hepatology*. 1994; 20(1 Pt 1):39–45.
5. Kirchner, SG, et al. Infantile hepatic hemangioendothelioma with subsequent malignant degeneration. *Pediatr Radiol*. 1981; 11(1):42–45.
6. Dehner, LP, et al. Vascular tumors of the liver in infants and children. A study of 30 cases and review of the literature. *Arch Pathol*. 1971; 92(2):101–111.

Angiosarcoma

KEY FACTS

Terminology

- Most common primary hepatic sarcoma

Etiology/Pathogenesis

- 25-40% of cases associated with vinyl chloride, Thorotrast, arsenic, or steroids

Clinical Issues

- Predominantly older patients, strong male predominance
- Liver biopsy may result in bleeding and death
- Best treatment option is surgery with adjuvant therapy

Microscopic

- Proliferation of malignant endothelial cells in vascular structures
  - Eventually destroys hepatic parenchyma
  - Solid, epithelioid, and spindled areas may be present
- Immunopositive for vascular markers: CD31, CD34, factor VIII
- Nuclear staining for transcription factors FLI-1 and ERG helps in confirming endothelial differentiation

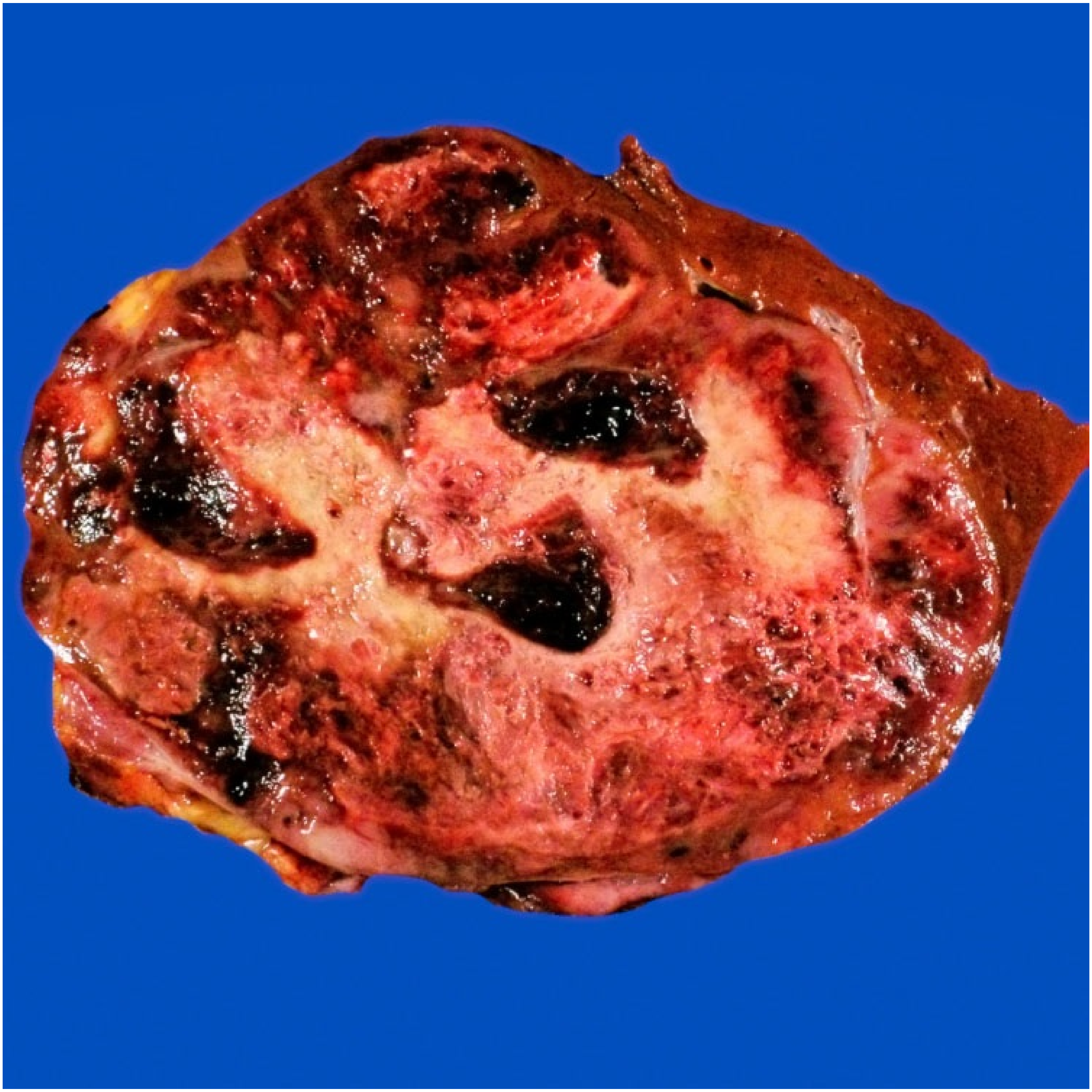
Ancillary Tests

- High Ki-67 (> 10%), diffuse p53 and diffuse MYC staining favors angiosarcoma over benign vascular tumors

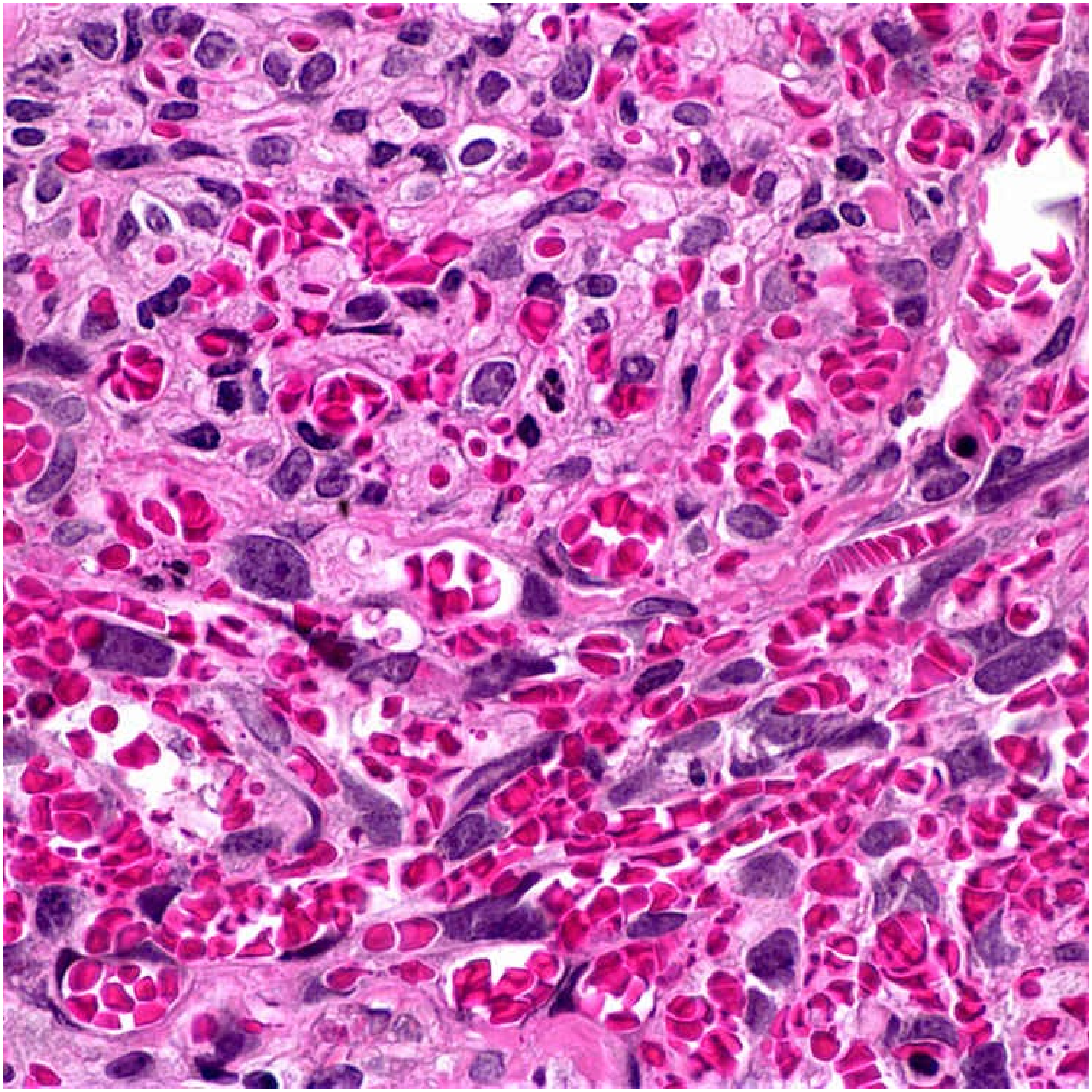
Top Differential Diagnoses

- Epithelioid hemangioendothelioma
- Carcinoma

• Other sarcomas
• Hepatic small vessel neoplasm

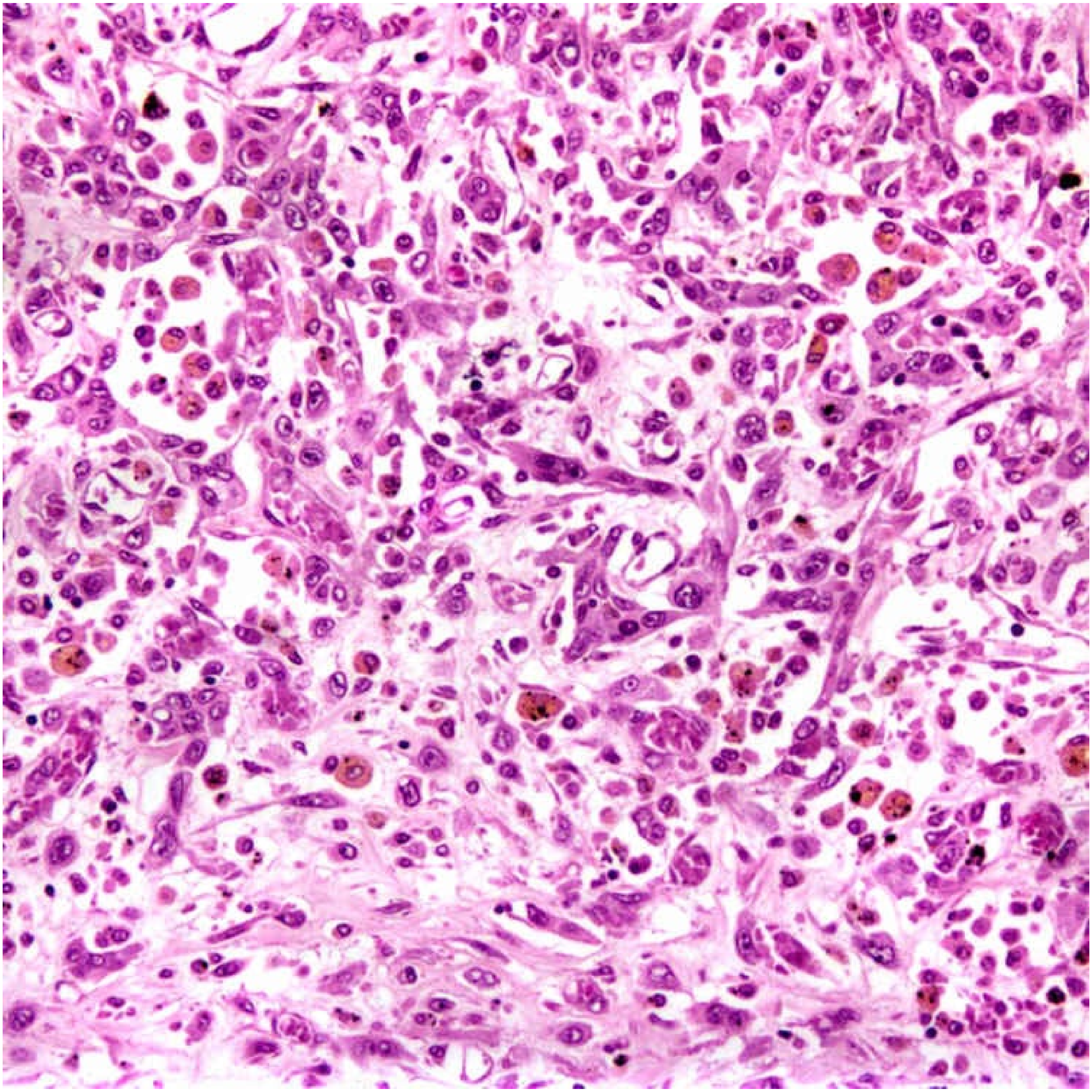


Hemorrhagic Cystic Tumor
This cross section from a partial hepatectomy for angiosarcoma shows numerous cystic, blood-filled spaces. [Courtesy C. Trower, PA (ASCP) and A. Folpe, MD.]

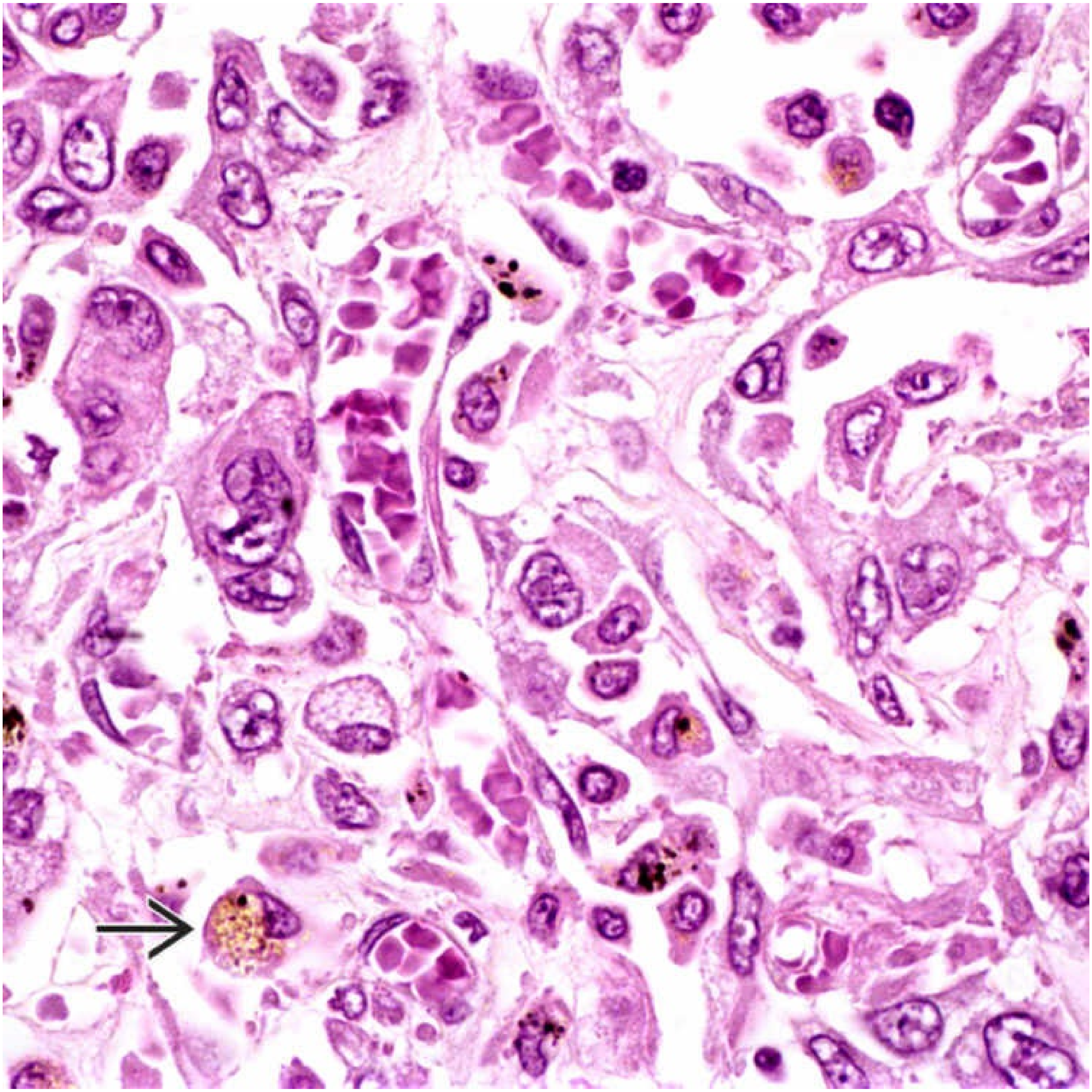


Spindled Tumor Cells

This angiosarcoma has a spindled growth pattern. The tumor cells are admixed with red blood cells and forming vascular lumina in some places. The normal hepatic architecture is no longer apparent.



Atypical Epithelioid Cells
Markedly atypical neoplastic endothelial cells line poorly formed vascular spaces. Note that the normal hepatic architecture has been destroyed.



Marked Cytologic Atypia
This angiosarcoma shows markedly atypical endothelial cells with enlarged, bizarre nuclei. The tumor cells show scattered vascular differentiation. Note the admixed red blood cells and hemosiderin-laden macrophages →.

TERMINOLOGY

Definitions

- Rare malignant vascular tumor of liver
  - Most common primary hepatic sarcoma
  - ~ 2% of malignant liver tumors

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Drugs: Androgens, contraceptive steroids, diethylstilbestrol, phenelzine
  - Toxins: Vinyl chloride, arsenic, copper sulfate, Thorotrast
  - ~ 25-40% of cases associated with vinyl chloride, Thorotrast, arsenic, or steroids
  - Many of these agents no longer used or strictly controlled
  - Long latency period of up to several decades after exposure

CLINICAL ISSUES

Epidemiology

- Age
  - Peak incidence in 6th-7th decades
  - Rare cases in children, formerly considered to be type 2 infantile hemangioemdothelioma
- Sex
  - M:F = 3:1

Presentation

- Signs and symptoms are nonspecific
  - Abdominal pain &/or distension
  - Hepatomegaly or palpable mass
  - Jaundice, ascites, weakness, fatigue, weight loss

Laboratory Tests

- Mild elevation of liver enzymes and bilirubin
  - Decreased albumin, increased PT
- α-fetoprotein and CEA are not elevated
- Anemia, leukocytosis, thrombocytopenia common

Treatment

- Best treatment option is surgery with adjuvant therapy
- > 80% of cases may be inoperable at presentation
- Transarterial chemoembolization used as palliation for unresectable cases

Prognosis

- Most patients die of liver failure within 1 year
  - Liver biopsy may result in bleeding and death
  - Numerous complications related to vascular nature of tumor
  - GI and intraabdominal bleeding
  - Vascular shunts involving tumor

- Metastases common to lung, bone, lymph nodes, spleen

IMAGING

Radiographic Findings

- CT and angiography: Hypervascular tumors with heterogeneous early and progressive enhancement

MACROSCOPIC

General Features

- Liver often markedly enlarged
  - Usually multicentric
  - Both lobes involved
  - Tumor nodules range from barely visible to many centimeters
- Red-brown, spongy, hemorrhagic cut surface

MICROSCOPIC

Histologic Features

- Proliferation of malignant endothelial cells
  - Enlarged, pleomorphic, hyperchromatic nuclei
  - Solid, epithelioid, and spindled areas can be present
  - Mitoses frequent
- Tumor infiltrates preexisting vascular structures
  - Dilated sinusoids filled with malignant endothelial cells
    - Papillary cell clusters, blood, necrotic debris may be seen
  - Progressive atrophy and disappearance of liver parenchyma
  - Tumor may invade and occlude central veins or portal venules

ANCILLARY TESTS

Immunohistochemistry

- Positive for CD31, CD34, factor VIII, FLI-1, ERG
- Staining may be weak or absent in poorly differentiated tumors
- High Ki-67 (> 10%), diffuse p53, and diffuse MYC staining favors angiosarcoma over benign vascular tumors

DIFFERENTIAL DIAGNOSIS

Epithelioid Hemangioendothelioma

• Less nuclear atypia, prominent stroma
• Characteristic zonation and infiltrative growth pattern

Carcinoma

• Absence of endothelial markers
• Diffuse strong keratin staining favors carcinoma, but keratin can be positive in angiosarcoma

Other Sarcomas

• Positive staining with endothelial markers confirms angiosarcoma

Bacillary Angiomatosis

• Abundant inflammation, no significant cytologic atypia
• Associated with *Bartonella* infection

Hepatic Small Vessel Neoplasm

• Rare tumor composed of small vessels
• Infiltrative border can mimic angiosarcoma
• Absence of cytologic atypia and low Ki-67 (< 10%) helps in diagnosis

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

• Historically, 25-40% are associated with drug/toxin exposure
• Liver biopsy may result in bleeding and death

SELECTED REFERENCES

1. Gill, RM, et al. Hepatic small vessel neoplasm, a rare infiltrative vascular neoplasm of uncertain malignant potential. *Hum Pathol*. 2016. [ePub].
2. Zhu, YP, et al. Primary hepatic angiosarcoma: a report of two cases and literature review. *World J Gastroenterol*. 2015; 21(19):6088–6096.
3. Zheng, YW, et al. Primary hepatic angiosarcoma and potential treatment options. *J Gastroenterol Hepatol*. 2014; 29(5):906–911.
5. Popper, H, et al. Development of hepatic angiosarcoma in man induced by vinyl chloride, thorotrast, and arsenic. Comparison with cases of unknown etiology. *Am J Pathol*. 1978; 92(2):349–376.

4. Neshiwat, LF, et al. Hepatic angiosarcoma. *Am J Med*. 1992; 93(2):219–222.
6.Mark, L, et al. Clinical and morphologic features of hepatic angiosarcoma in vinyl chloride workers. *Cancer*. 1976; 37(1):149–163.

Mesenchymal Hamartoma

KEY FACTS

Etiology/Pathogenesis

- Developmental anomaly vs. neoplasm
- Recurrent balanced translocation involving chromosome band 19q13.4 or 19q13.3
- Association with uniparental disomy

Clinical Issues

- Typically occurring in 1st 2 years of life, rarely seen in adults
- Excellent prognosis after complete excision
- Malignant transformation in rare case reports

Macroscopic

- Large, solid, &/or cystic hepatic lesion
- Typically solitary, rarely multifocal

Microscopic

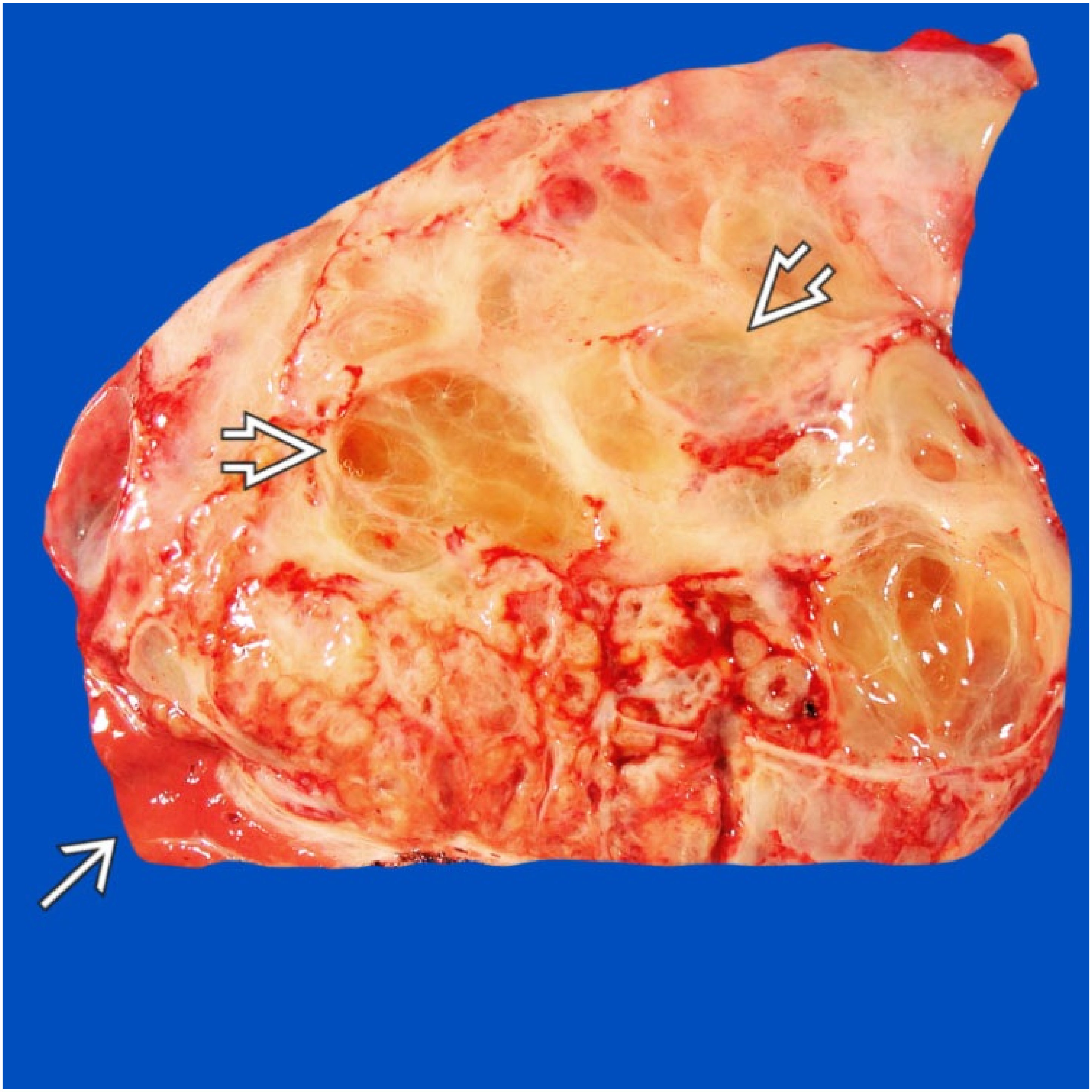
- Mixture of varying portions of mesenchymal cells, bile ducts, hepatocytes, blood vessels, and cystic spaces
- Variant features like prominent myxoid stroma, minimal ductular component, and lack of cystic component may be seen in older children and adults
- Cystic spaces of varying size are common
- Cysts lack lining epithelium, likely represent degenerative phenomenon

Ancillary Tests

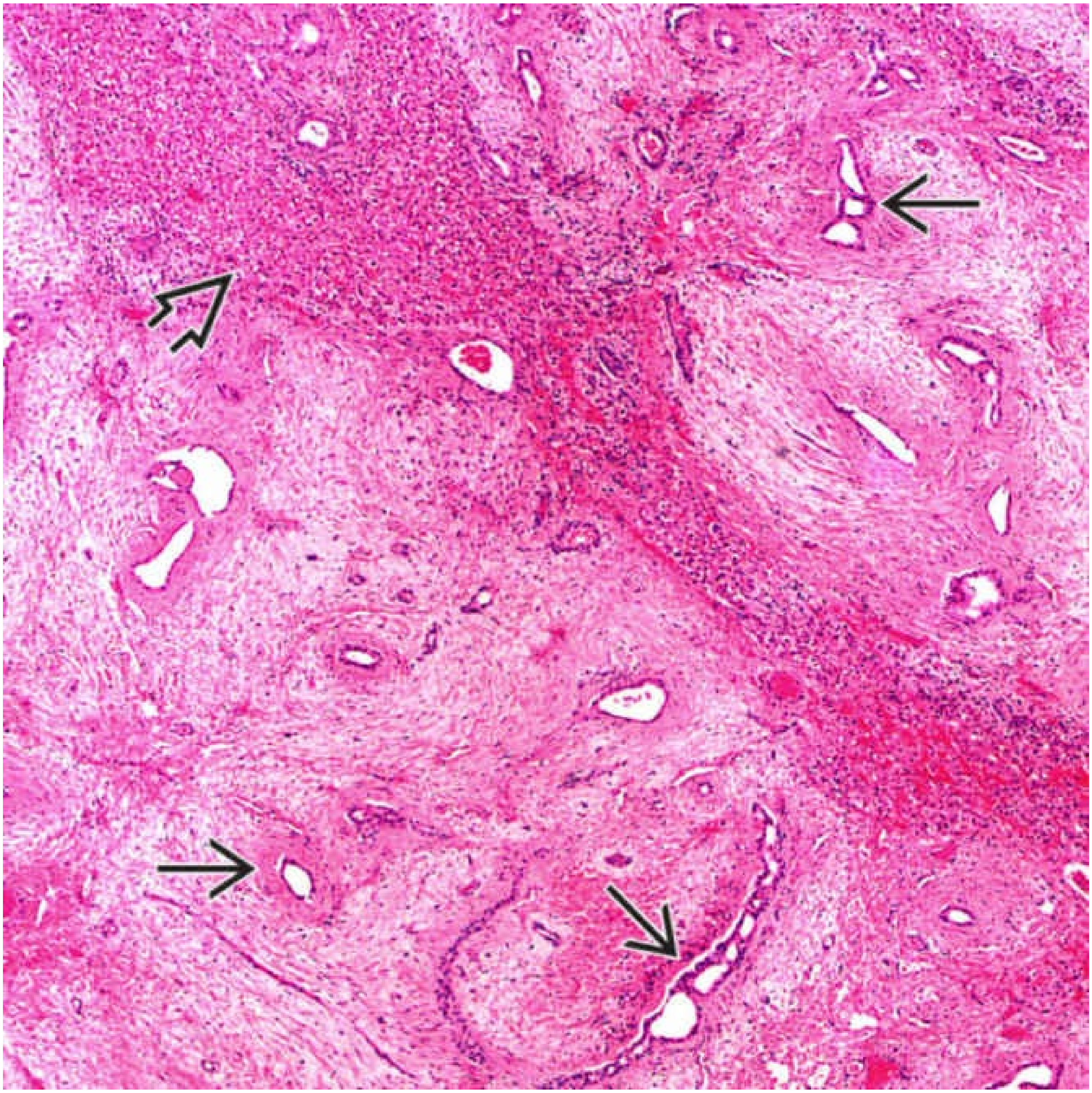
- Mesenchyme: Positive for vimentin, smooth muscle actin and desmin
- Glypican-3: Can be positive in hepatocytes and less commonly in mesenchymal component

Top Differential Diagnoses

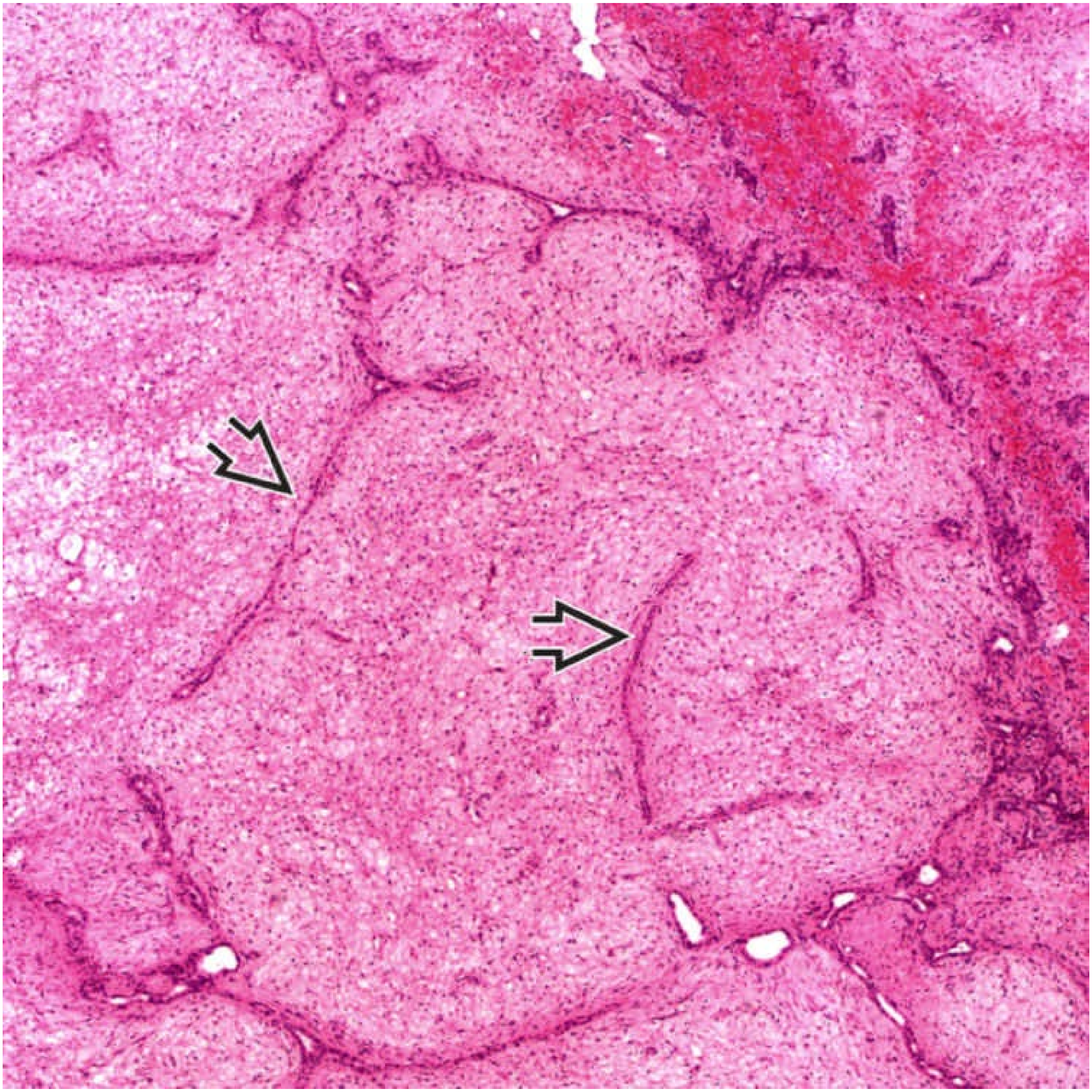
- Hepatoblastoma
- Infantile hemangioendothelioma



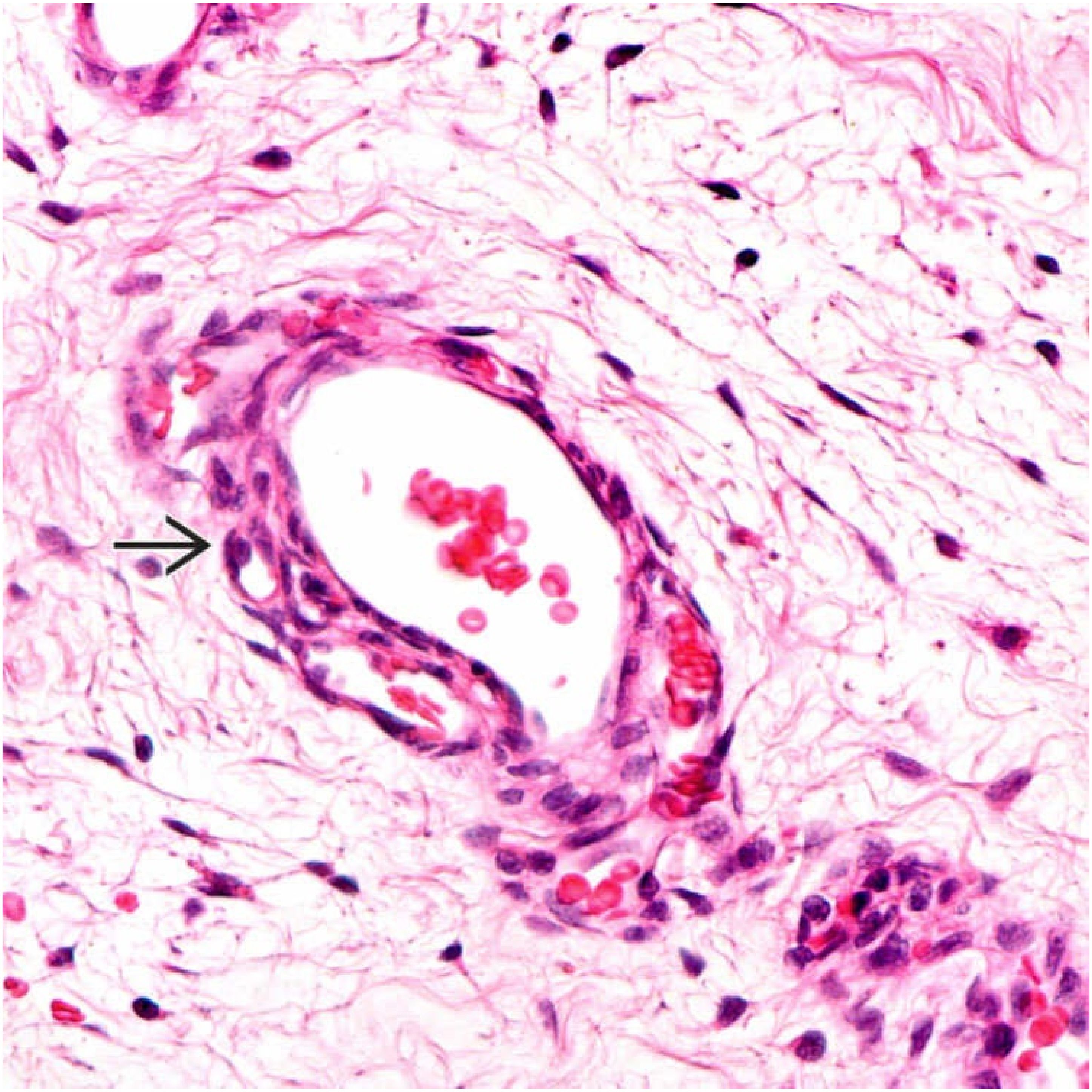
Gross Appearance
The cut surface shows numerous variably sized cystic spaces admixed with solid areas. Minimal uninvolved liver tissue is present at the resection margin .



Loose Myxoid Stroma
Low-power view shows numerous bile ducts → in a loose, myxoid mesenchymal stroma. Note the presence of a large island of normal-appearing hepatocytes ⇨ in the tumor.



Branching Bile Ducts
Compressed and branching bile ducts within collagenous stroma have a ductal plate malformation-like pattern ➯ .



Stellate Stromal Cells
High-power view shows scattered stellate mesenchymal cells loosely embedded in an edematous stroma. Note the presence of blood vessels →.

TERMINOLOGY

Definitions

• Benign tumor primarily occurring in young children

ETIOLOGY/PATHOGENESIS

Unknown

- Presumed developmental malformation of primitive hepatic mesenchyme
  - Occurs late in embryogenesis
  - Postnatal growth largely due to cystic degeneration
- Evidence for neoplastic nature
  - Balanced translocation involving same breakpoint at chromosome band 19q13.4 or 19q13.3
- Association with androgenetic-biparental mosaicism (ABM)
  - ABM implies diploid chromosomal complement derived entirely from father in subset of cells
  - ABM also predisposes to placental mesenchymal dysplasia, which has been associated with MH
- Both abnormalities are thought to lead to activation of chromosome 19 microRNA cluster in hepatic stroma

CLINICAL ISSUES

Epidemiology

- Incidence
  - ~ 5% of pediatric liver tumors
- Age
  - Usually in 1st 2 years of life, < 5% after age of 5
  - Rarely seen in adults
- Sex
  - Male predominance in pediatric cases
  - Female predominance in adult cases

Presentation

- Painless abdominal mass
- Sudden abdominal distention due to rapid fluid accumulation in tumor

Laboratory Tests

- Normal or mildly elevated liver tests
- Moderately elevated serum α-fetoprotein level

Treatment

- Surgical resection

Prognosis

- Excellent after complete excision
- Occasional spontaneous regression
- Rare transformation to undifferentiated embryonal sarcoma

IMAGING

General Features

- Hypodense, hypovascular, solid or multicystic lesion
- Can be detected prenatally by ultrasound and MR

MACROSCOPIC

General Features

- Typically solitary, rarely multifocal
  - Pedunculated in 20% of cases, 75% involve right lobe
  - Usually attached to inferior surface of liver
- Few cm to > 30 cm in size
- Solid &/or cystic
  - Solid areas: White, yellow, or tan
  - Cysts: Few mm to 14 cm
    - Clear to yellow fluid, or gelatinous material

MICROSCOPIC

Histologic Features

- Mixture of varying components of mesenchymal cells, bile ducts, hepatocytes, blood vessels, and cystic spaces
  - Mesenchymal cells
  - Spindled or stellate fibroblasts and myofibroblasts
  - Edematous, myxoid, collagenous, or hyalinized stroma
  - No pleomorphism, mitoses, or necrosis
- Bile ducts
  - May be dilated, tortuous, compressed, branching, or arranged in ductal-plate-malformation pattern
  - Lined by cuboidal or atrophic biliary epithelium
  - Neutrophil infiltration may be seen
  - Surrounded by loose mesenchyme or dense collagen
- Hepatocytes
  - Large islands, small clusters, or thin compressed strips
  - More abundant at periphery of tumor
  - Cytologically normal, may show reactive changes
  - Preserved cell plates, lacks normal acinar architecture
- Blood vessels
  - Numerous arteries, veins, and capillaries throughout
  - Thick-walled vessels may be prominent at periphery
- Cystic spaces
  - Lymphangioma-like but lacking endothelial lining
  - Likely representing cystic degeneration of loose, primitive mesenchyme

- Absence of normal portal tracts
- Foci of extramedullary hematopoiesis may be seen
- Irregular tumor border without true capsule
- Variant features like prominent myxoid stroma, minimal ductular component, and lack of cystic component may be seen in older children and adults

ANCILLARY TESTS

Immunohistochemistry

- Mesenchyme positive for vimentin, smooth muscle actin, and desmin
- Bile ducts positive for cytokeratins 7 and 19
- Hepatocytes positive for Hep-Par1
- Glypican-3 can be positive in hepatocytes and less commonly in mesenchymal component

DIFFERENTIAL DIAGNOSIS

Hepatoblastoma

- Fetal &/or embryonal patterns
- Much higher cellularity
- Cartilaginous and osteoid-like mesenchymal elements

Infantile Hemangioendothelioma

- Small intercommunicating vascular channels
- Plump endothelial cells, endothelial markers

SELECTED REFERENCES

1. Kapur, RP, et al. Activation of the chromosome 19q microRNA cluster in sporadic and androgenetic-biparental mosaicism-associated hepatic mesenchymal hamartoma. *Pediatr Dev Pathol*. 2014; 17(2):75–84.
3. Sugito, K, et al. Mesenchymal hamartoma of the liver originating in the caudate lobe with t(11;19)(q13;q13.4): report of a case. *Surg Today*. 2010; 40(1):83–87.
4. Stringer, MD, et al. Mesenchymal hamartoma of the liver: a systematic review. *J Pediatr Surg*. 2005; 40(11):1681–1690.

2. Levy, M, et al. Expression of glypican-3 in undifferentiated embryonal sarcoma and mesenchymal hamartoma of the liver. *Hum Pathol*. 2012; 43(5):695–701.
5. Yesim, G, et al. Mesenchymal hamartoma of the liver in adulthood: immunohistochemical profiles, clinical and histopathological features in two patients. *J Hepatobiliary Pancreat Surg*.

2005; 12(6):502–507.

Undifferentiated Embryonal Sarcoma

KEY FACTS

Etiology/Pathogenesis

- Rare cases of undifferentiated embryonal sarcoma (UES) arising in mesenchymal hamartoma
- Share same chromosome translocation involving 19q13.4
- Postulated that UES is malignant counterpart of mesenchymal hamartoma

Clinical Issues

- 6-13% of all primary hepatic tumors in childhood
- > 50% occurring from 6-10 years of age
- Rarely seen in middle-aged and elderly patients
- Improved survival in recent years with combined modality therapy
- Neoadjuvant and adjuvant chemotherapy, radiotherapy

Microscopic

- Spindle, oval, or stellate tumor cells loosely or compactly distributed in myxoid or fibrous stroma
- Marked nuclear pleomorphism and hyperchromasia with frequent multinucleated or bizarre giant cells and brisk mitotic activity
- Characteristic PAS-positive, diastase-resistant cytoplasmic and extracellular eosinophilic globules

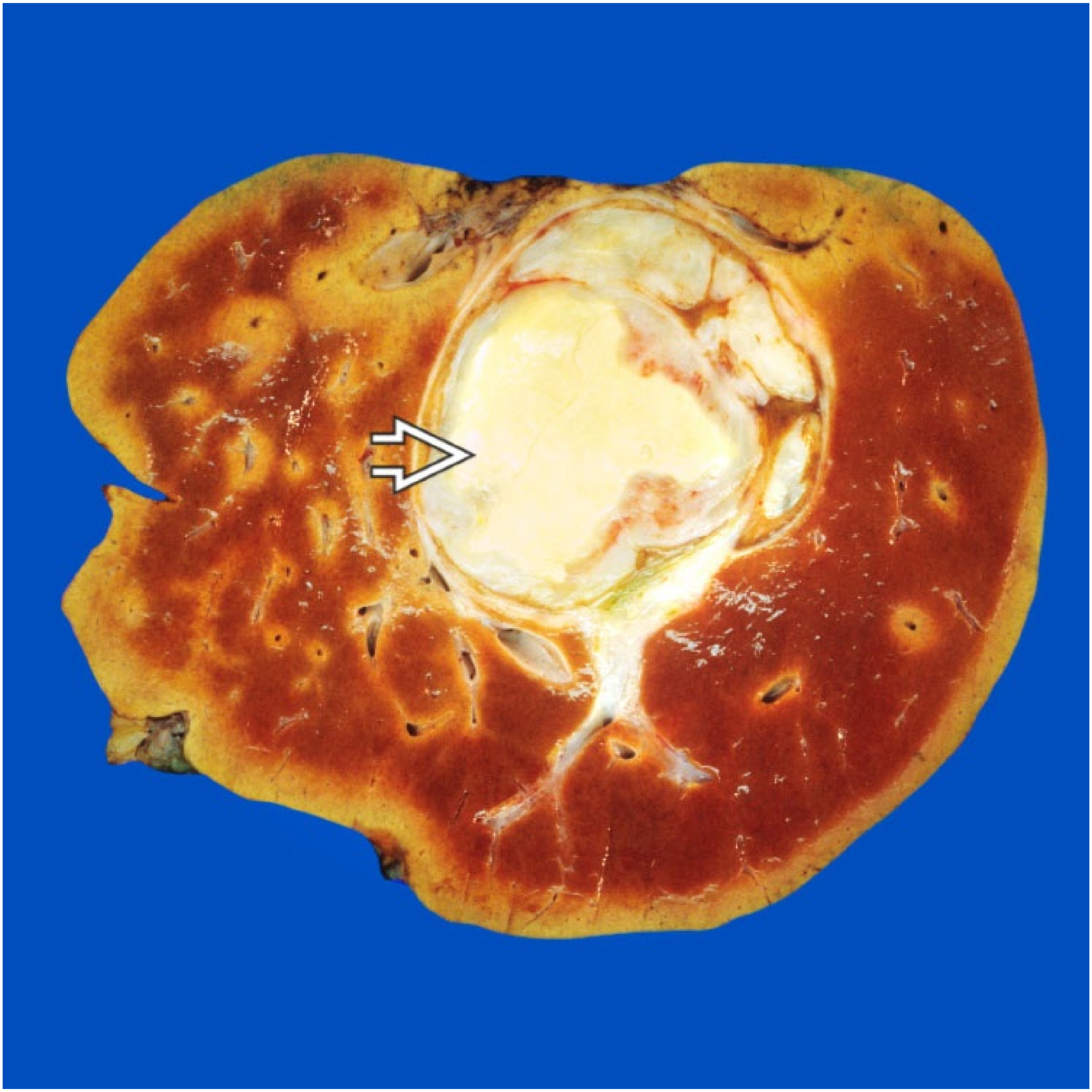
Ancillary Tests

- Diffusely positive for vimentin, α-1-antitrypsin, and α-1-antichymotrypsin
- Eosinophilic globules stain with α-1-antitrypsin, α-1-antichymotrypsin, vimentin, immunoglobulins, and albumin

Top Differential Diagnoses

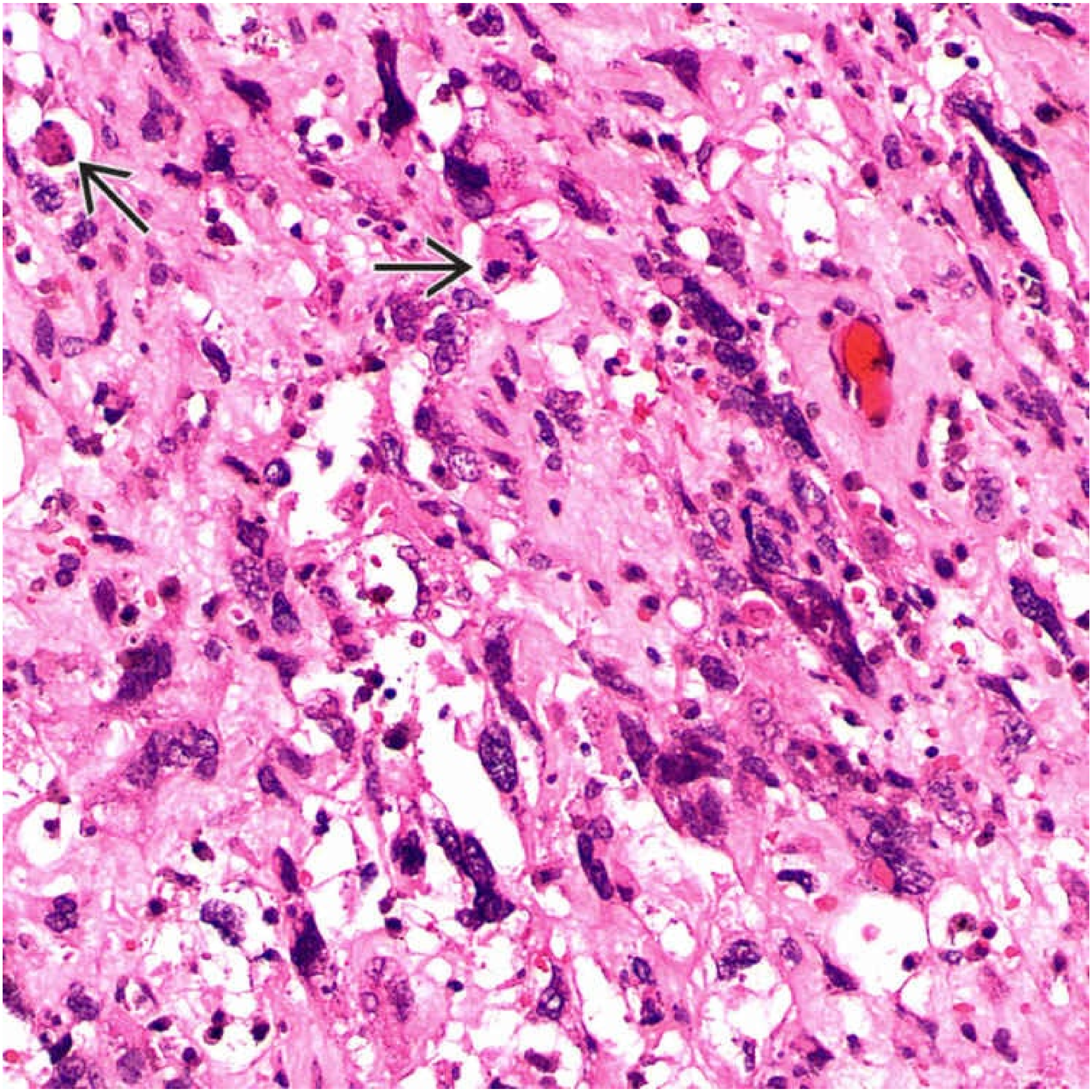
- Embryonal rhabdomyosarcoma
- Metastatic gastrointestinal stromal tumor

• Sarcomatoid carcinoma

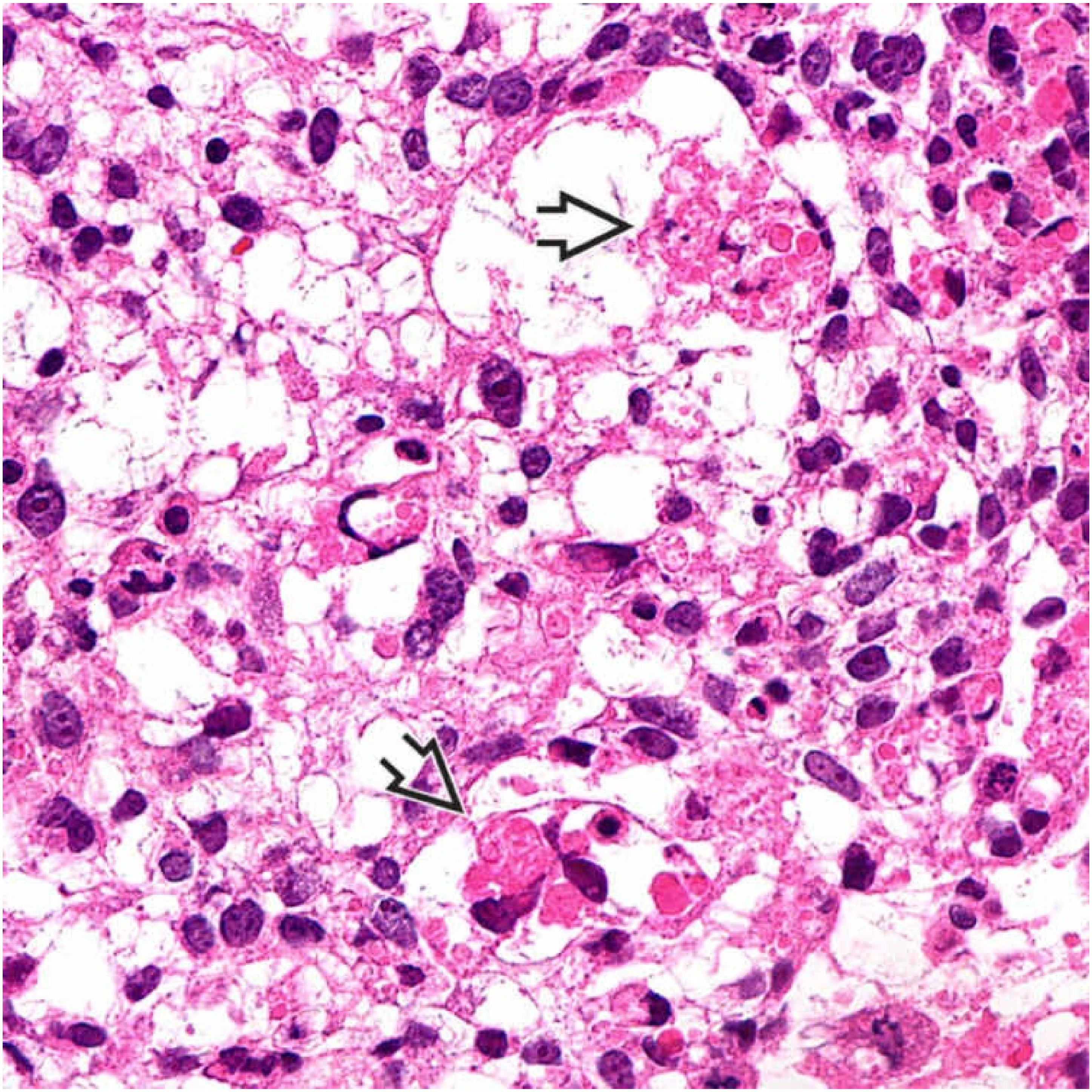


Embryonal Carcinoma

Gross photograph shows a well-demarcated liver mass with a compressed pseudocapsule. The cut surface is variegated with admixed solid areas and a large area of yellow necrosis ⇨ .

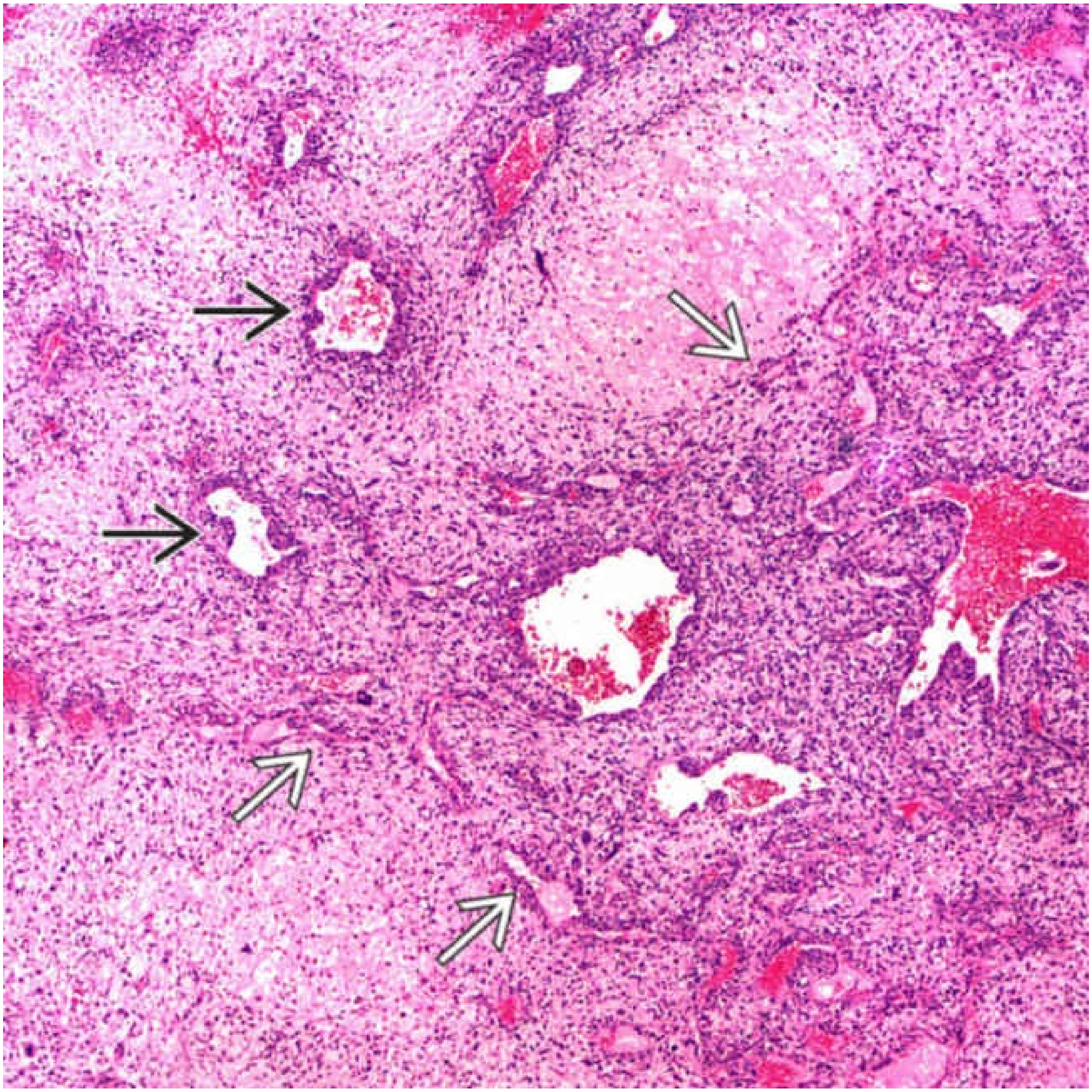


Marked Nuclear Pleomorphism
High-power view shows markedly pleomorphic tumor cells separated by a fibrous stroma. Note the presence of apoptotic tumor cells →.



Hyaline Globules

High-power view shows ovoid tumor cells with minimal intervening stroma. Numerous cytoplasmic and extracellular eosinophilic globules are seen ⇨ .



Undifferentiated Embryonal Carcinoma Arising in Mesenchymal Hamartoma
A case of undifferentiated embryonal carcinoma arising in mesenchymal hamartoma shows the presence of numerous bile ducts →, some arranged in a ductal plate malformation-like pattern ⇒.

TERMINOLOGY

Abbreviations

- Undifferentiated embryonal sarcoma (UES)

Synonyms

- Embryonal sarcoma
- Undifferentiated sarcoma
- Malignant mesenchymoma

Definitions

- Malignant tumor of liver composed of primitive mesenchymal cells with partial, divergent differentiation

ETIOLOGY/PATHOGENESIS

Unknown

- Rare cases of UES arising in mesenchymal hamartoma
- Share same chromosome translocation involving 19q13.4

CLINICAL ISSUES

Epidemiology

- Incidence
  - 6-13% of all primary hepatic tumors in childhood
- Age
  - Usually occurring from 5-20 years
  - Rarely seen in middle-aged and elderly patients
- Sex
  - M = F

Presentation

- Abdominal distention, pain, palpable mass
- Weight loss, fever

Laboratory Tests

- Normal or mildly elevated liver enzymes, usually alkaline phosphatase
- Normal serum α-fetoprotein level

Treatment

- Surgical resection
- Neoadjuvant and adjuvant chemotherapy, radiotherapy

Prognosis

- Markedly improved survival in recent years with combined modality therapy
  - Survival of ≥ 5 years in some patients (median survival < 1 year in 1980s)
- Local recurrence common even with complete excision and adjuvant chemotherapy
- Distant metastasis infrequent; most common in lungs, pleura, peritoneum

IMAGING

General Features

- Heterogeneous mass with solid and cystic components
- Difficult to distinguish from mesenchymal hamartoma

MACROSCOPIC

General Features

- Predilection for right lobe
- Solitary, well demarcated, unencapsulated; 9-30 cm in size
- Variegated cut surface with solid areas alternating with gelatinous cystic areas and foci of necrosis and hemorrhage

MICROSCOPIC

Histologic Features

- Spindle, oval, or stellate tumor cells loosely or compactly distributed in myxoid or fibrous stroma
- Marked nuclear pleomorphism and hyperchromasia with frequent multinucleated or bizarre giant cells
- Pink granular cytoplasm with ill-defined cell borders
- Multiple variably sized, PAS-positive, diastase-resistant cytoplasmic and extracellular eosinophilic globules
- Brisk mitoses, tumor necrosis can be extensive
- Intratumoral hemorrhage common
- Foci of extramedullary hematopoiesis may be seen
- Entrapped hepatocytes and bile ducts at periphery

ANCILLARY TESTS

Immunohistochemistry

- Diffusely positive for vimentin, α-1-antitrypsin, and α-1-antichymotrypsin
    - Focally positive for glypican-3, smooth muscle actin, muscle-specific actin, desmin, CD34, S100, calponin, CK-PAN, CD10, CD68, Bcl-2, p53
    - Dot-like reactivity with CK-PAN and membrane staining with CD56 has been reported
- Ki-67 proliferation index: 30-95%
- Eosinophilic globules stain with α-1-antitrypsin, α-1-antichymotrypsin, vimentin, immunoglobulins, and albumin

DIFFERENTIAL DIAGNOSIS

Embryonal Rhabdomyosarcoma

- Usually arises in extrahepatic biliary tree
- Rhabdomyoblasts with cross striations
- Immunostains for muscle markers are positive

Metastatic Gastrointestinal Stromal Tumor

- Clinical history of gastrointestinal primary
- Usually not in children
- Positive for C-kit, DOG1

Sarcomatoid Carcinoma

- Immunostains for hepatocellular carcinoma or cholangiocarcinoma
- Usually not in children

SELECTED REFERENCES

1. Pérez-Gómez, RM, et al. Diffuse membranous immunoreactivity of CD56 and paranuclear dot-like staining pattern of cytokeratins AE1/3, CAM5.2, and OSCAR in undifferentiated (embryonal) sarcoma of the liver. *Appl Immunohistochem Mol Morphol*. 2010; 18(2):195–198.
2. Lenze, F, et al. Undifferentiated embryonal sarcoma of the liver in adults. *Cancer*. 2008; 112(10):2274–2282.
3. Pachera, S, et al. Undifferentiated embryonal sarcoma of the liver: case report and literature survey. *J Hepatobiliary Pancreat Surg*. 2008; 15(5):536–544.
4. Zheng, JM, et al. Primary and recurrent embryonal sarcoma of the liver: clinicopathological and immunohistochemical analysis. *Histopathology*. 2007; 51(2):195–203.

Hepatectomy Specimen Handling

TERMINOLOGY

Partial Hepatectomy

- Ranges from removal of small wedge to lobe or more
- Typically consists of lesion plus variably sized rim of nonneoplastic liver parenchyma

Liver Explant

- Result of liver transplantation
  - Tumors
    - Goals of evaluation are to assess margins and stage tumor
  - Medical liver disease
    - Goal of evaluation is to determine or confirm cause of liver disease &/or liver failure

MACROSCOPIC

Specimen Handling

- Partial hepatectomy
  - Determine what procedure was performed
    - Including exactly what structures/organs are present
  - Orient specimen
    - May require surgeon’s assistance
  - Identify surgical margin (exposed, cauterized, cut surface of hepatic parenchyma) and ink it
  - Specimen dimensions
    - Weight
    - Measurements
  - Examine external surface
    - Bulges and areas of serosal retraction may indicate tumors
    - Resection for trauma may have capsular lacerations, similar to spleen

- Make initial slice through center of tumor, perpendicular to resection margin
- Continue to thinly serially section specimen perpendicular to margin, parallel to initial slice
– Identify closest approach of tumor(s) to margin and take these sections
– Examine all cut surfaces for additional lesions
- Document all lesions
– Location
– Size
– Circumscription
– Color
– Consistency
– Note necrosis, scarring, or hemorrhage
- If patient has received preoperative ablative therapy, describe areas of necrosis vs. grossly viable tumor
– Sections of tumor(s) should demonstrate relationship of tumor to surrounding liver and margin
– Interface between nonneoplastic liver and tumor are important and often less necrotic
– Primary tumors should be sampled more extensively than known metastases
- Search for vascular invasion
– Document and sample if present grossly
– Document tumor thrombi
- Examine and describe nonneoplastic hepatic parenchyma and take sections
– Note especially if there is background of cirrhosis
– Take sections of nonneoplastic liver away from tumor mass
- Examine lymph nodes if present

- Liver explant
  - Determine what procedure was performed
    – Note exactly what structures/organs are present
  - Orient liver
    – Identify right and left lobes (best viewed from above)

– Caudate lobe is between portal vein and inferior vena cava; best viewed from below
– Quadrate lobe is between gallbladder fossa and ligamentum teres, separated from caudate lobe by inferior vena cava; best viewed from below
– Porta hepatis contains bile duct, hepatic artery, portal vein, nerves, lymphatics

- ○ Specimen dimensions
  – Weight
  – Measurements
    - ☐ Measure gallbladder too, if present
- ○ Examine external surface
  – Document any abnormalities/lesions
- ○ Identify porta hepatis 1st
  – Document if tumor involves structures at portal hepatis and if tumor is at margin of these structures
    - ☐ Specifically document if tumor is at margin of any of these structures
  – Look for thrombi in vessels
  – Submit complete cross section of all structures
    - ☐ Portal vein, bile duct, hepatic artery
  – Identify hepatic veins and submit section
  – In cases of biliary disease, extrahepatic bile duct may be hard to find
    - ☐ Can insert probe into intrahepatic duct near hilum and work backward
  – Look for hilar lymph nodes
- ○ Submit section of soft tissue and liver perpendicular to hilum
  – Allows evaluation of larger bile ducts and peribiliary glands
- ○ Evaluate gallbladder
  – Describe and section as per routine cholecystectomy
- ○ Section liver perpendicular to its long axis with long, sharp knife
  – Record color and consistency of liver parenchyma
  – Describe any focal lesions
    - ☐ Transplant teams will often want to compare lesions seen preoperatively by imaging with what is found at pathologic evaluation
  – Submit sections
    - ☐ Right lobe-3
    - ☐ Left lobe-3
    - ☐ Caudate lobe-1
    - ☐ Quadrate lobe-1
    - ☐ Any focal lesions
    - ☐ Any other areas with distinct appearance

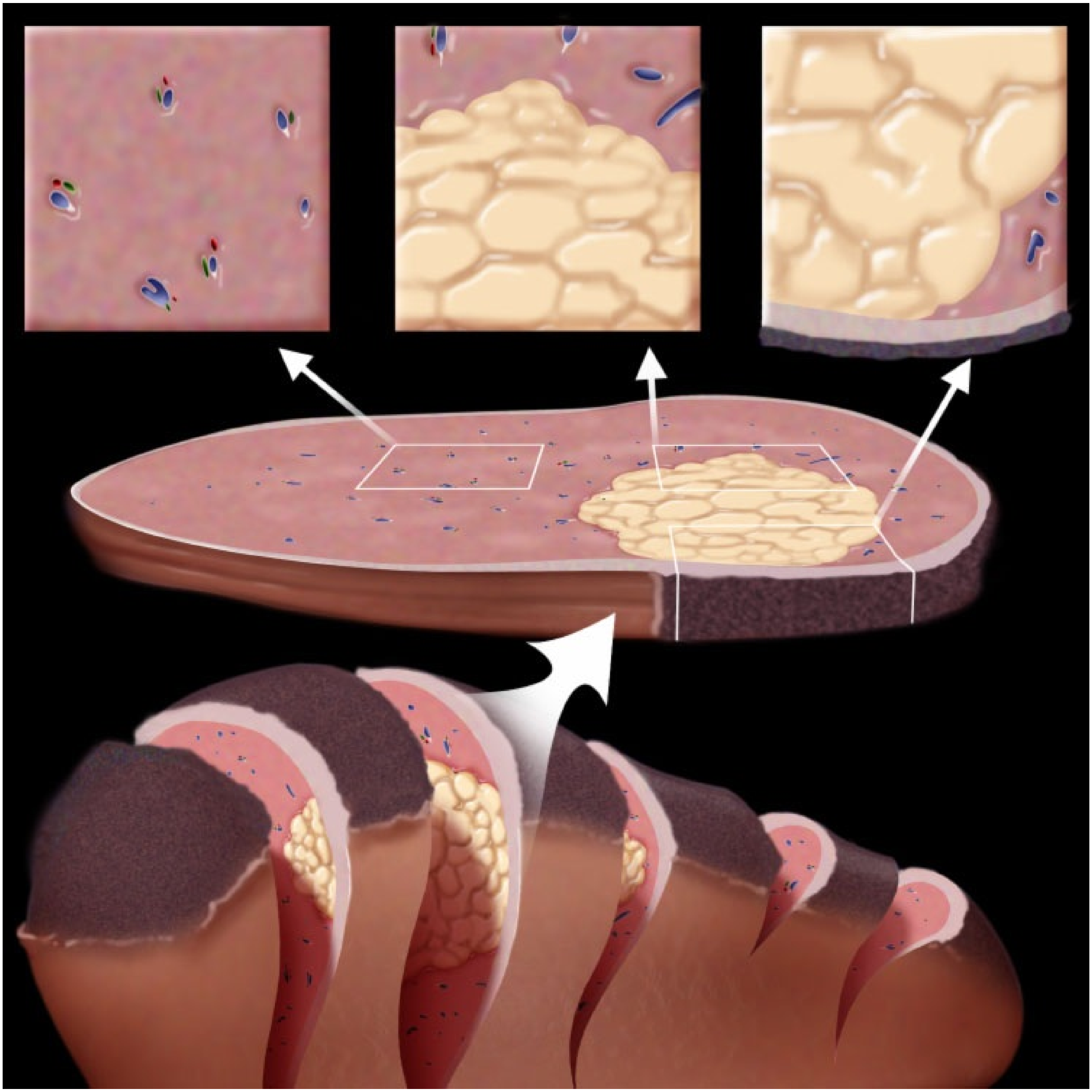
Anatomic Features

- Liver has dual blood supply
  - ○ Portal vein
  – Carries blood away from intestines and pancreas
  – Enters liver at porta hepatis

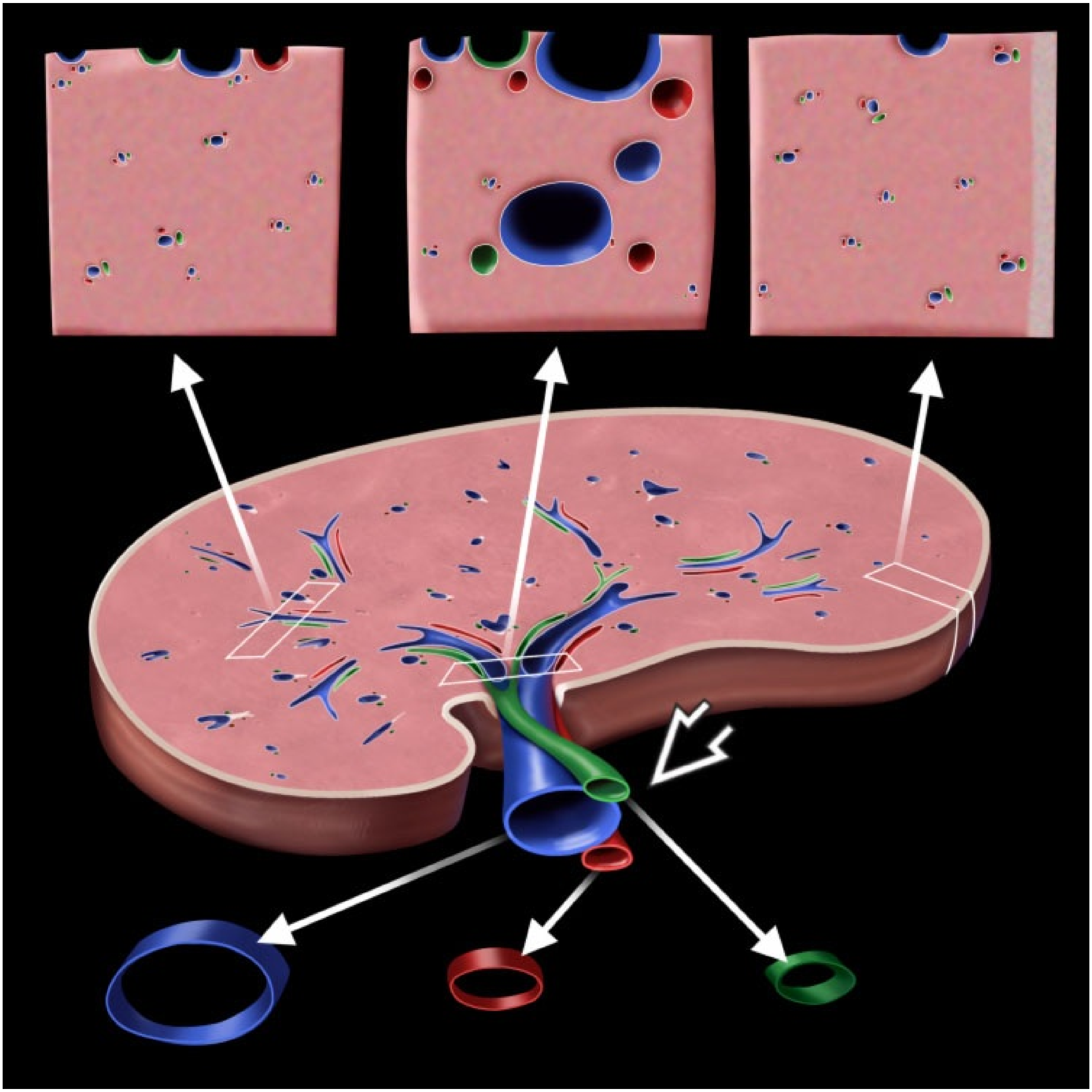
○ Hepatic artery

– Supplies oxygen-rich blood from celiac axis
– Enters liver at porta hepatis

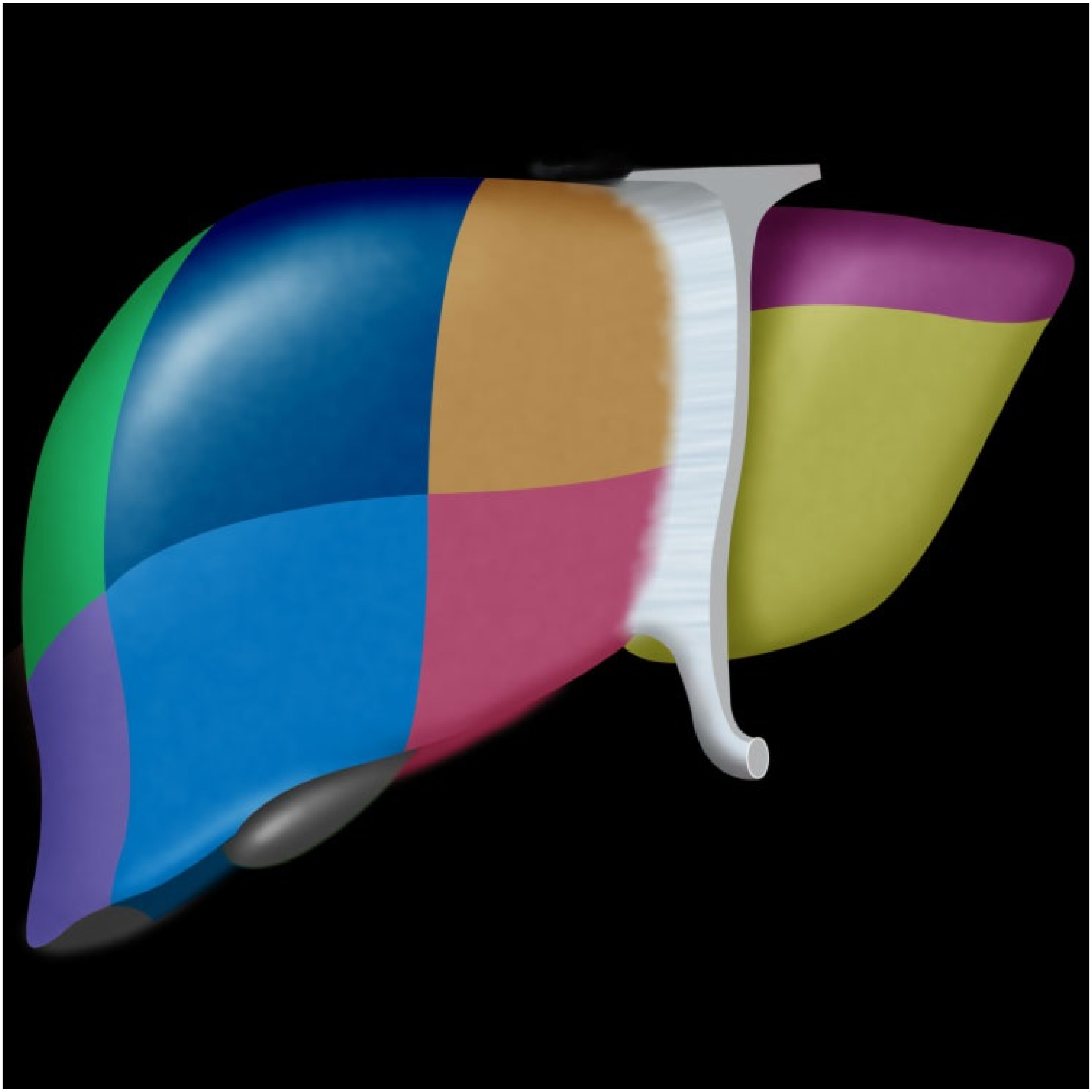
- Hepatic veins
  - Right, middle, and left hepatic veins drain liver and enter vena cava
- Bile ducts
  - Follow courses of hepatic artery and portal vein through liver
  - Nourished by hepatic arteries via peribiliary plexus
  - Bile is formed in hepatocytes, secreted into canaliculi and eventually into bile ducts
- Lymphatics
  - Capsule and stroma of liver are rich in lymphatics
  - Hepatic lymphatics exit at porta hepatis
  - Drain primarily to hepatic nodes along hepatic artery and celiac nodes
- Anatomic divisions
  - Right lobe lateral to falciform ligament
  - Left lobe medial to falciform ligament
  - Caudate and quadrate lobes
  - 8 functional segments are served by their own vascular pedicles and branches of biliary tree
    – More important anatomy in terms of surgical approaches
- Superior, anterior, and lateral surfaces are smooth and covered by peritoneum
  - Except for “bare area” below diaphragm
- Falciform and round ligaments connect liver to abdominal wall



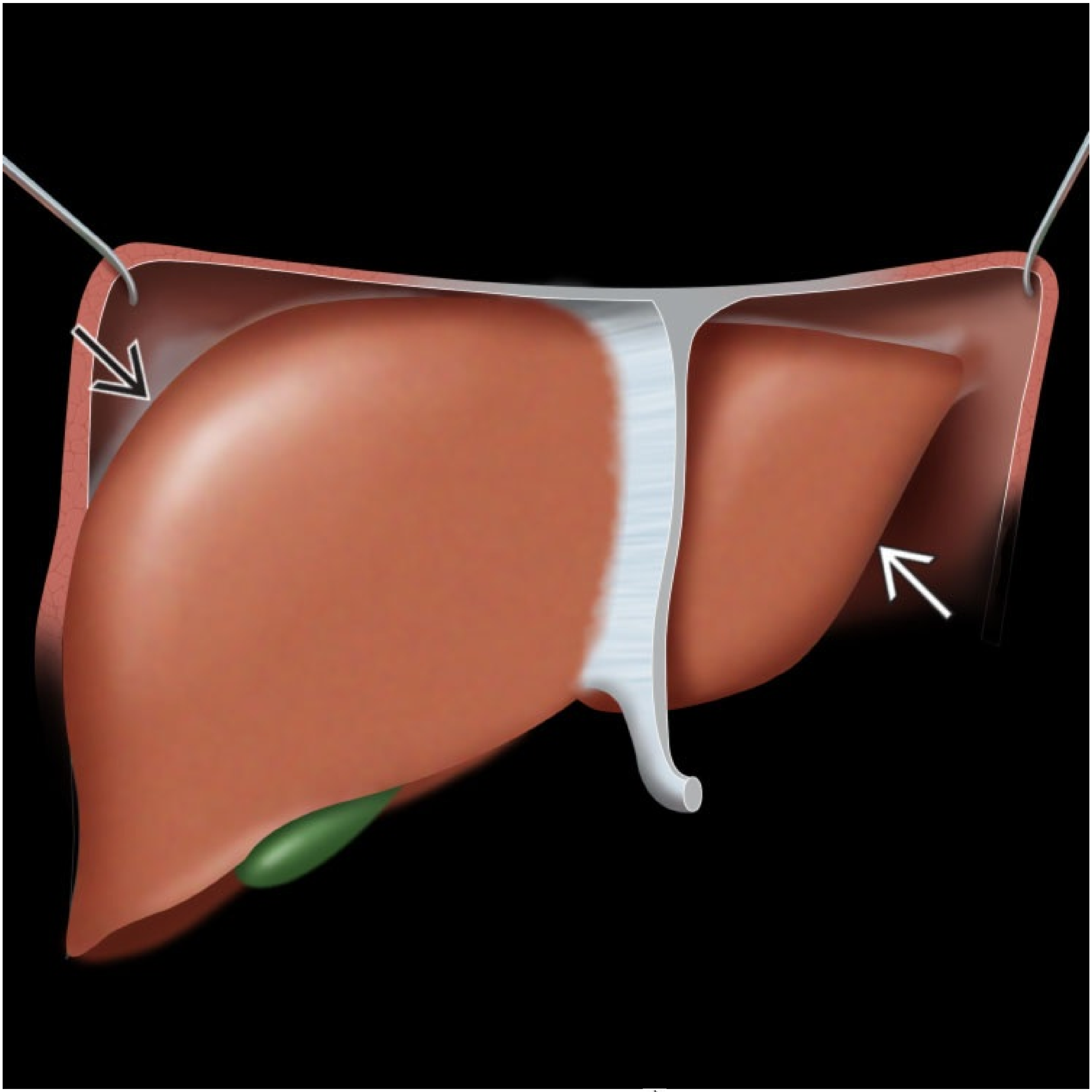
Sections From Partial Hepatectomy
Important sections from a partial hepatectomy include tumor and margin (right), tumor/nonneoplastic liver interface (center), and nonneoplastic liver (left).



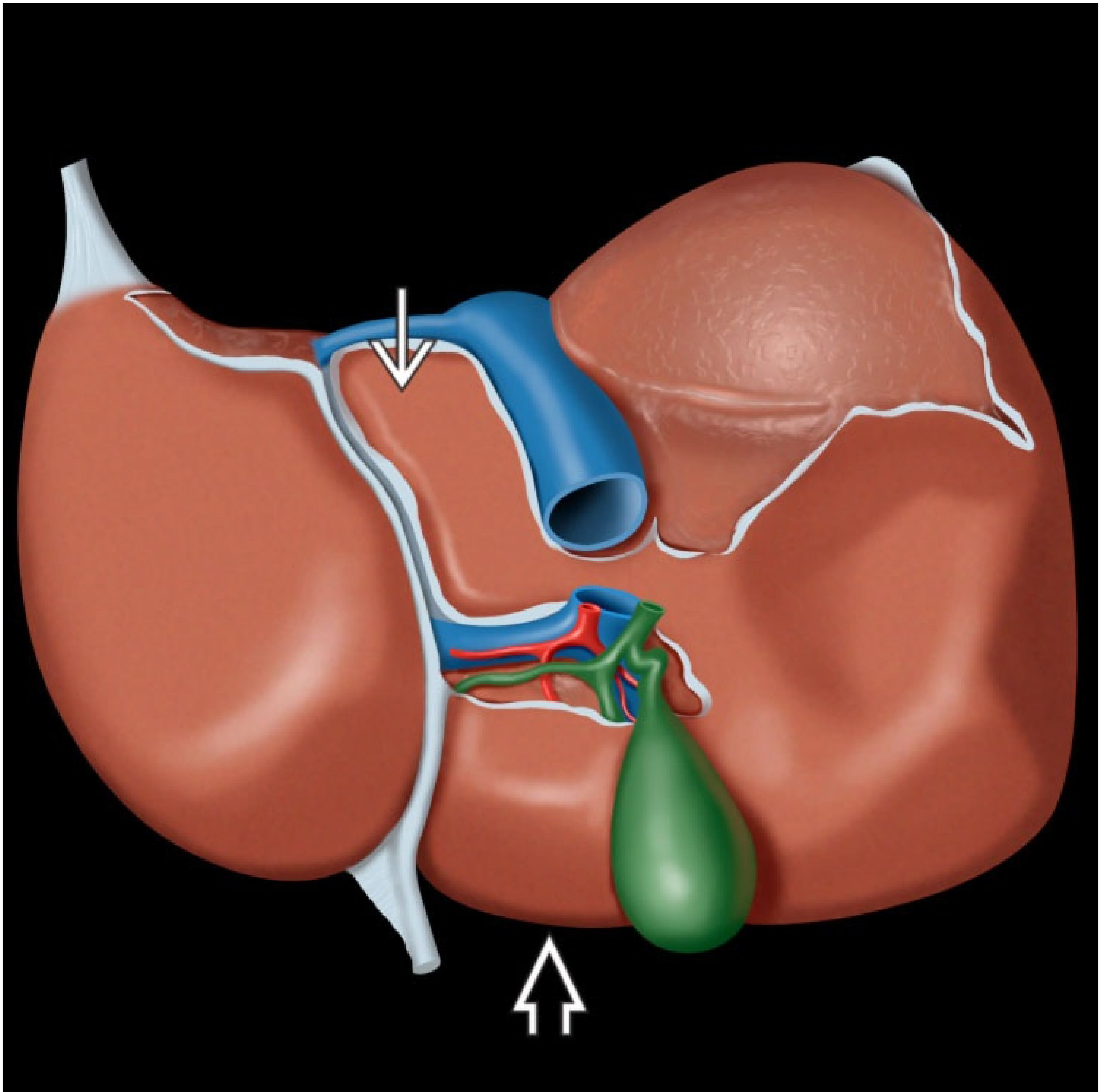
Sections From Explant
Important sections from an explant include a shave margin of the porta hepatis ⇨, a section of hilum (center), and sections of parenchyma (left and right).



Functionally, the liver is divided into 8 segments. These segments, more than the lobar anatomy, are relevant to the planning of surgical resections.



In order to orient the liver, it is important to identify the right lobe → lateral to the falciform ligament and the left lobe medial to the falciform ligament ⇨ .



Viewed from below, the quadrate lobe is between the gallbladder fossa and the ligamentum teres ⇨, and the caudate lobe ⇨ is between the portal vein and the inferior vena cava.

SELECTED REFERENCES

1. Holland, AE, et al. Importance of small (< or = 20-mm) enhancing lesions seen only during the hepatic arterial phase at MR imaging of the cirrhotic liver: evaluation and comparison with whole explanted liver. *Radiology*. 2005; 237(3):938–944.
2. Torbenson, M. Liver. In: Westra WH, et al, eds. *Surgical Pathology Dissection: An Illustrated Guide*. 2nd ed. New York: Springer; 2003:76–81.
3. Qin, LX, et al. The prognostic significance of clinical and pathological features in hepatocellular carcinoma. *World J Gastroenterol*. 2002; 8(2):193–199.

4. Shirabe, K, et al. Intrahepatic cholangiocarcinoma: its mode of spreading and therapeutic modalities. *Surgery*. 2002; 131(1 Suppl):S159–S164.
5. Emond, JC, et al. Surgical anatomy of the liver and its application to hepatobiliary surgery and transplantation. *Semin Liver Dis*. 1994; 14(2):158–168.
6. Bismuth, H. Surgical anatomy and anatomical surgery of the liver. *World J Surg*. 1982; 6(1):3–9.

SECTION 10
MISCELLANEOUS HEPATIC DISORDERS

OUTLINE

Langerhans Cell Histiocytosis

KEY FACTS

Etiology/Pathogenesis

- Clonal proliferation of Langerhans cells
  - Evidence of genetic studies favors neoplastic process
  - Likely from bone marrow-derived myeloid dendritic precursors

Clinical Issues

- Affects infants and children, rarely adults
  - Unisystem disease most often involves bone followed by skin, lymph node, and lung
  - Multisystem disease is subdivided into low and high risk according to involvement of "risk" organs
  - High-risk organs: Liver, spleen, bone marrow
  - Liver involvement: 10-15%
  - Involvement of high-risk organs is associated with poorer prognosis

Microscopic

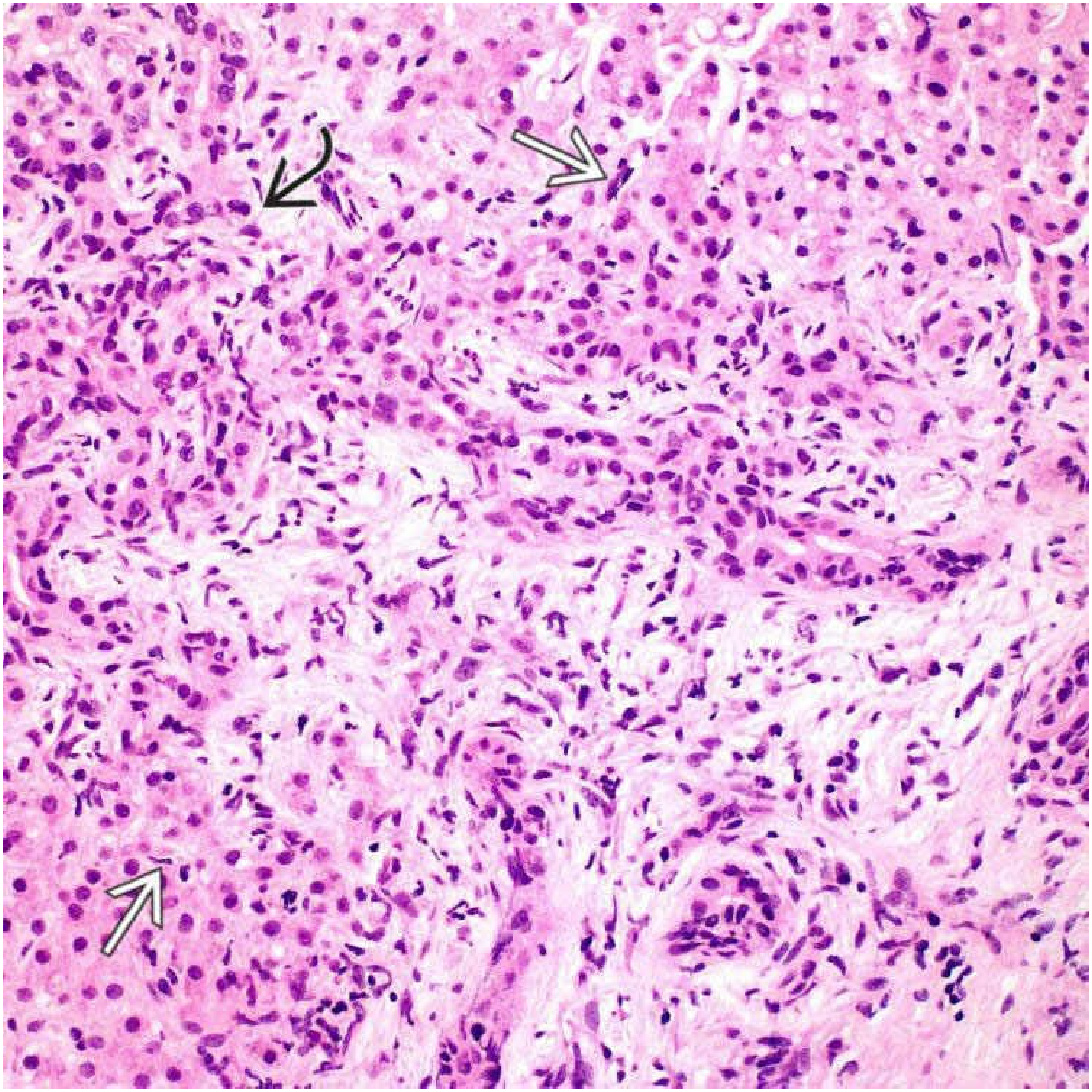
- Infiltration of portal tracts and lobules by Langerhans cells
  - May form small granulomatous nodules or large mass-like lesions
  - Langerhans cells typically show irregular and elongated nuclei, prominent nuclear grooves and folds, fine chromatin, indistinct nucleoli, abundant pink cytoplasm
  - Often accompanied by varying numbers of eosinophils, lymphocytes, neutrophils, plasma cells, non-Langerhans histiocytes
- Bile duct infiltration and destruction
  - Displacement or replacement of duct epithelial cells by Langerhans cells
  - Portal, periportal and periduct concentric fibrosis, duct loss, ductular reaction
  - May progress to biliary cirrhosis

Ancillary Tests

- Langerhans cells stain with S100, CD1a, langerin (CD207)

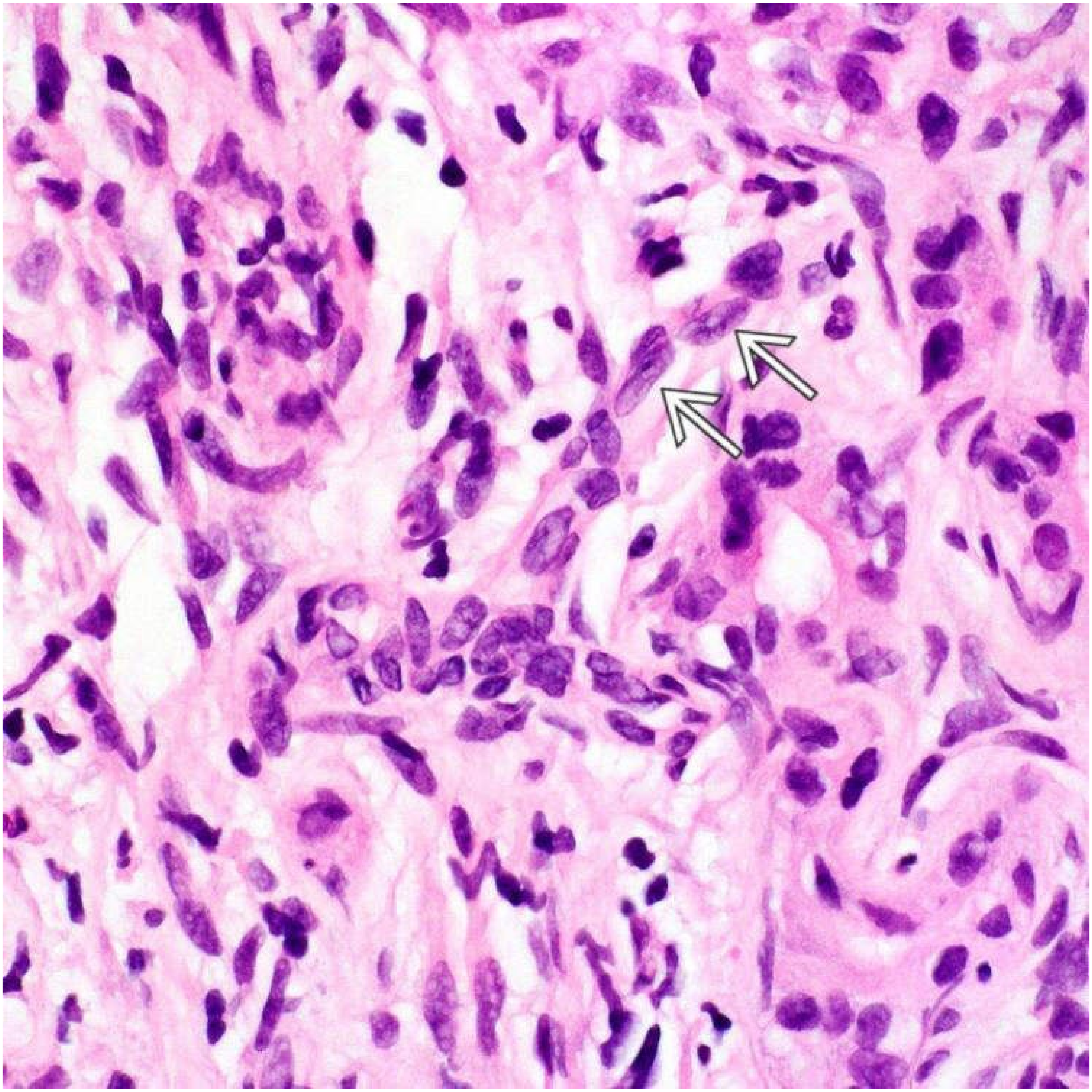
Top Differential Diagnoses

• Primary sclerosing cholangitis



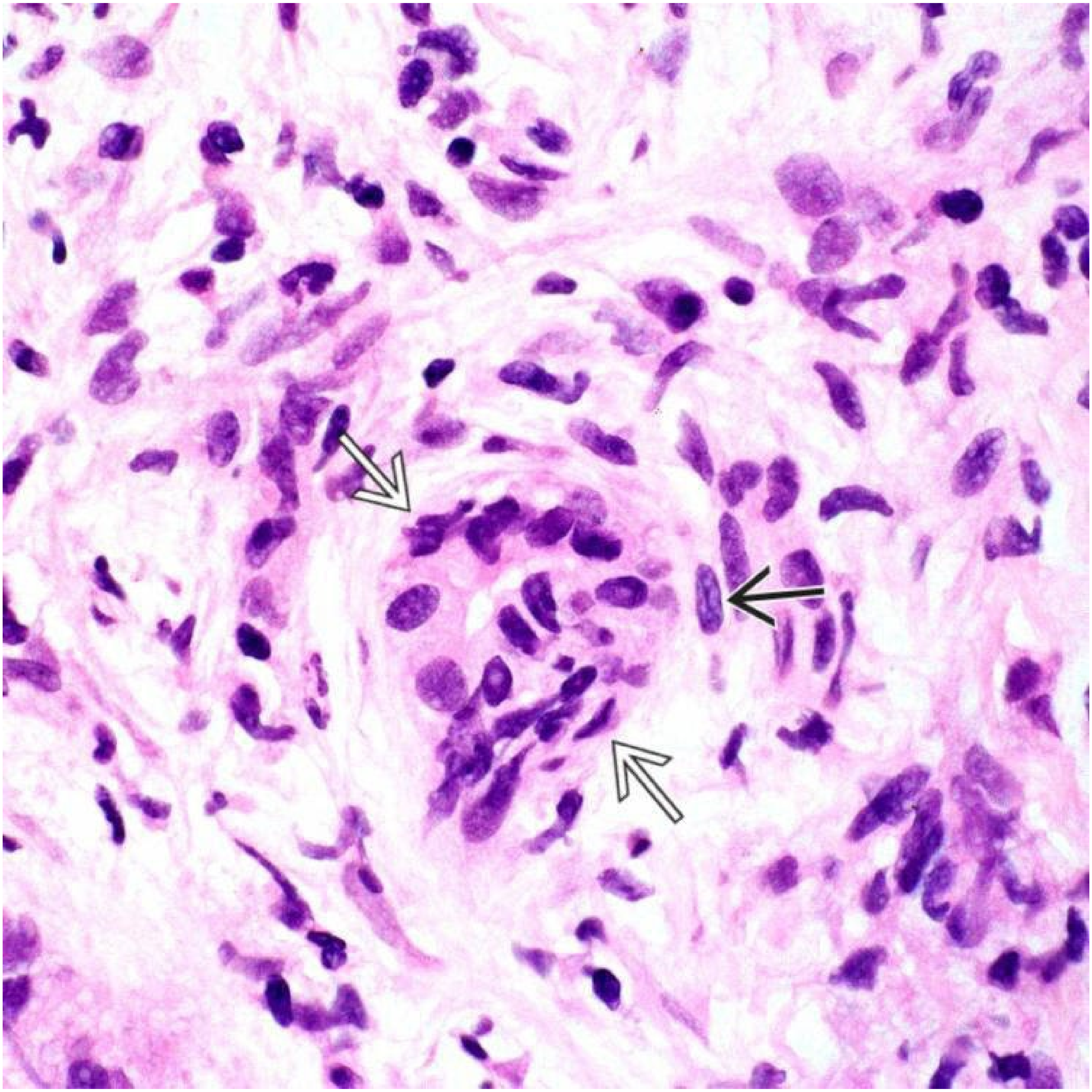
Hepatic Langerhans cell Histiocytosis

This liver biopsy from a 10-month-old girl with hepatomegaly shows markedly expanded portal tracts infiltrated by elongated Langerhans cells. The adjacent lobules are also infiltrated ⇒. Ductular reaction is evident ↷ .



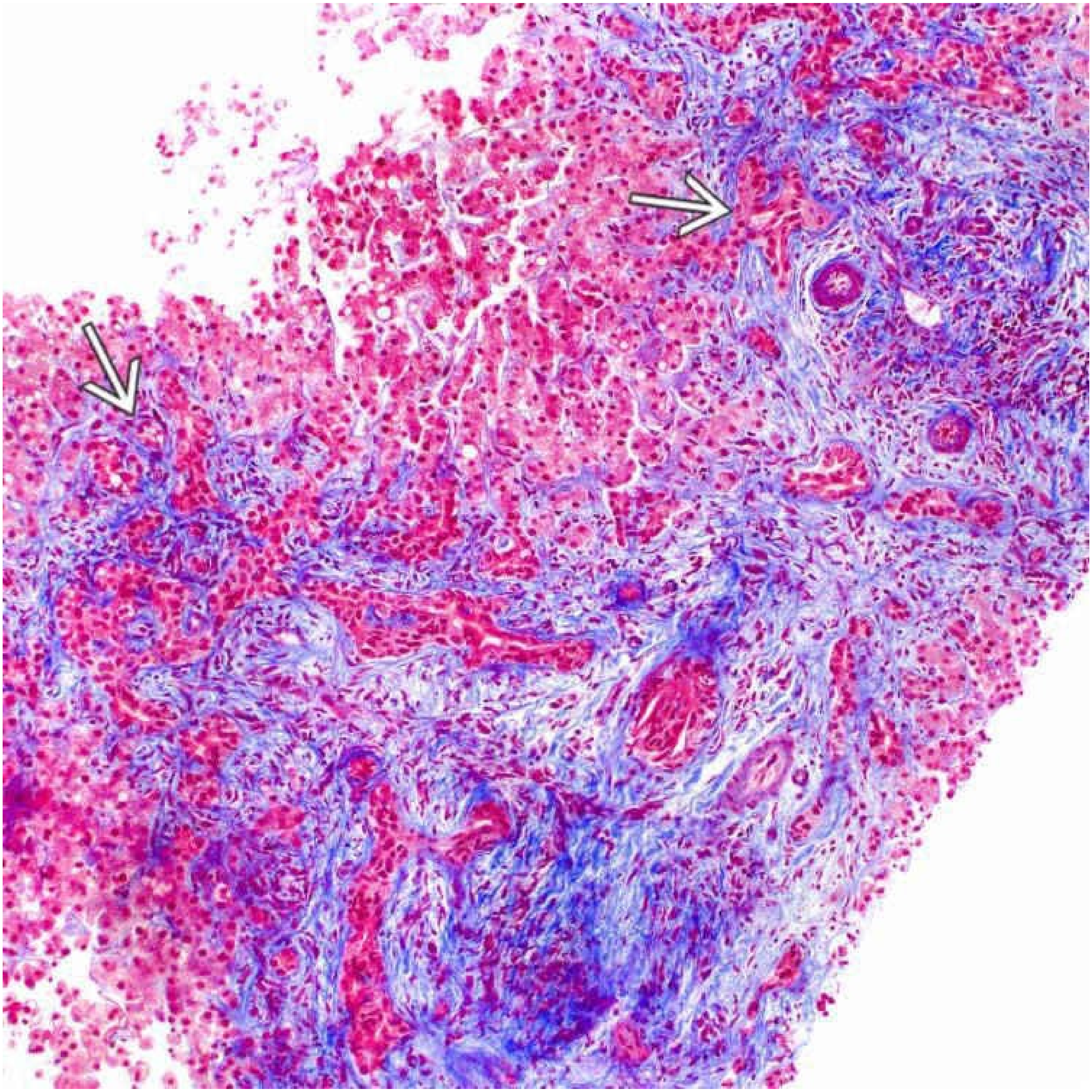
Langerhans Cells

Langerhans cells typically have irregular and elongated nuclei, fine chrome, indistinct nucleoli, and eosinophilic cytoplasm. Nuclear grooves or folds are appreciated in some cells ⇨. Scattered lymphocytes and rare neutrophils are seen in this portal tract.



Bile Duct Injury

This microphotograph shows a bile duct that is partially damaged by infiltrating Langerhans cells . Langerhans cells also infiltrate ductules (not shown in this field). Nuclear grooves are noted in some cells .



Fibrosis
Portal and periportal fibrosis is evident in this hepatic Langerhans cell histiocytosis case as highlighted by trichrome stain. Note the presence of prominent ductular reaction ⇒ .

TERMINOLOGY

Abbreviations

- Langerhans cell histiocytosis (LCH)

Synonyms

- Histiocytosis X

- Eosinophilic granuloma (unifocal LCH)
- Hans-Schüller-Christian disease (multifocal unisystem LCH)
- Letterer-Siwe disease (multifocal multisystem LCH)

Definitions

- Infiltration of liver by proliferating Langerhans cells

ETIOLOGY/PATHOGENESIS

Clonal Proliferation

- Evidence of genetic studies favors neoplastic process
  - *BRAF* V600E mutations seen in 25-64% of cases
  - *MAP2K1* mutations seen in 27.5% of cases

Cell Origin

- Likely from bone marrow-derived myeloid dendritic precursors

CLINICAL ISSUES

Epidemiology

- Incidence
  - 2-5 per million per year
- Age
  - Infants and children, rarely adults

Site

- Unisystem disease most often involves bone followed by skin, lymph node, and lung
  - Multisystem disease is subdivided into low and high risk according to involvement of "risk" organs
  - High-risk organs: Liver, spleen, bone marrow
    - Liver involvement: 10-15%
    - Rarely, liver involvement only

Presentation

- Hepatomegaly, jaundice, ascites

Natural History

- Early stage: Infiltration by Langerhans cells
- Late stage: Fibrosis, sclerosing cholangitis, biliary cirrhosis

Treatment

- Systemic chemotherapy
- Liver transplantation

Prognosis

- Very good overall survival
  - Involvement of high-risk organs is associated with poorer prognosis
  - ○ 3-year survival decreases from 96.7% to 51.8% with liver involvement
  - – Disease recurrence in transplanted livers in ~ 30% of cases
- ○ Lack of response to chemotherapy at 6 weeks predicts poor survival

IMAGING

General Features

- ERCP may show findings similar to primary sclerosing cholangitis

MACROSCOPIC

General Features

- May cause cystic dilation of large bile ducts
- May form mass-like lesions

MICROSCOPIC

Histologic Features

- Infiltration of portal tracts and lobules by Langerhans cells
  - May form small granulomatous nodules or large mass-like lesions
  - Langerhans cells typically show irregular and elongated nuclei, prominent nuclear grooves and folds, fine chromatin, indistinct nucleoli, abundant pink cytoplasm
  - Often accompanied by varying numbers of eosinophils, lymphocytes, neutrophils, plasma cells, non-Langerhans histiocytes
- Bile duct infiltration and destruction
  - Displacement or replacement of duct epithelial cells by Langerhans cells
  - Portal, periportal and periduct concentric fibrosis, duct loss, ductular reaction
  - Secondary sclerosing cholangitis may develop in ducts without direct Langerhans cell infiltration
  - May progress to biliary cirrhosis
  - Injury to large bile ducts may lead to cystic dilation and rupture with xanthogranulomatous response

ANCILLARY TESTS

Immunohistochemistry

- Langerhans cells stain with S100, CD1a, langerin (CD207)

Electron Microscopy

- Characteristic Birbeck granules: Tennis racket-shaped structures with striated appearance

DIFFERENTIAL DIAGNOSIS

Primary Sclerosing Cholangitis

- No evidence of multisystem LCH
- Frequent association with inflammatory bowel disease

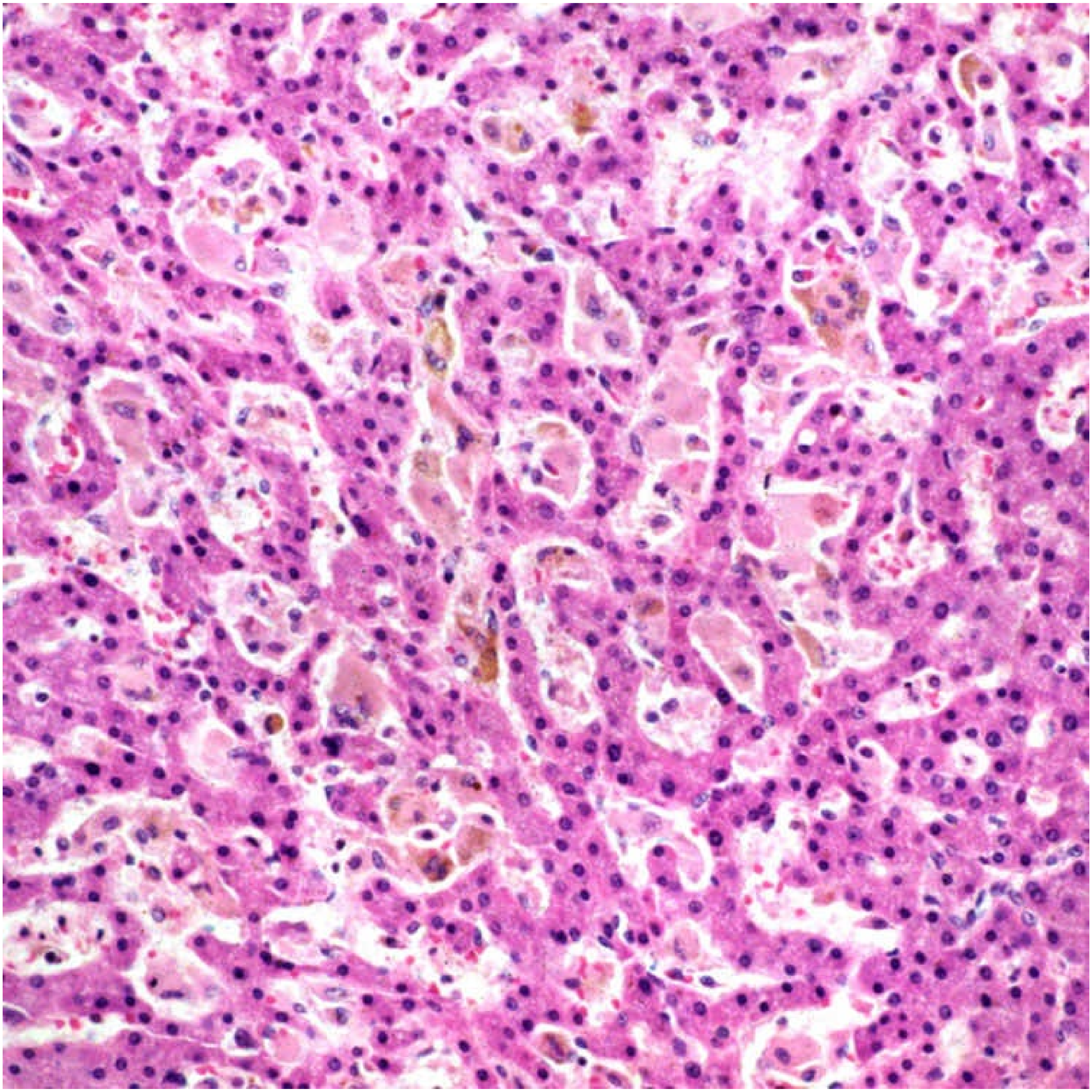
Biliary Atresia

- Absence of extrahepatic bile ducts and gallbladder
- More pronounced ductular reaction, bile plugs

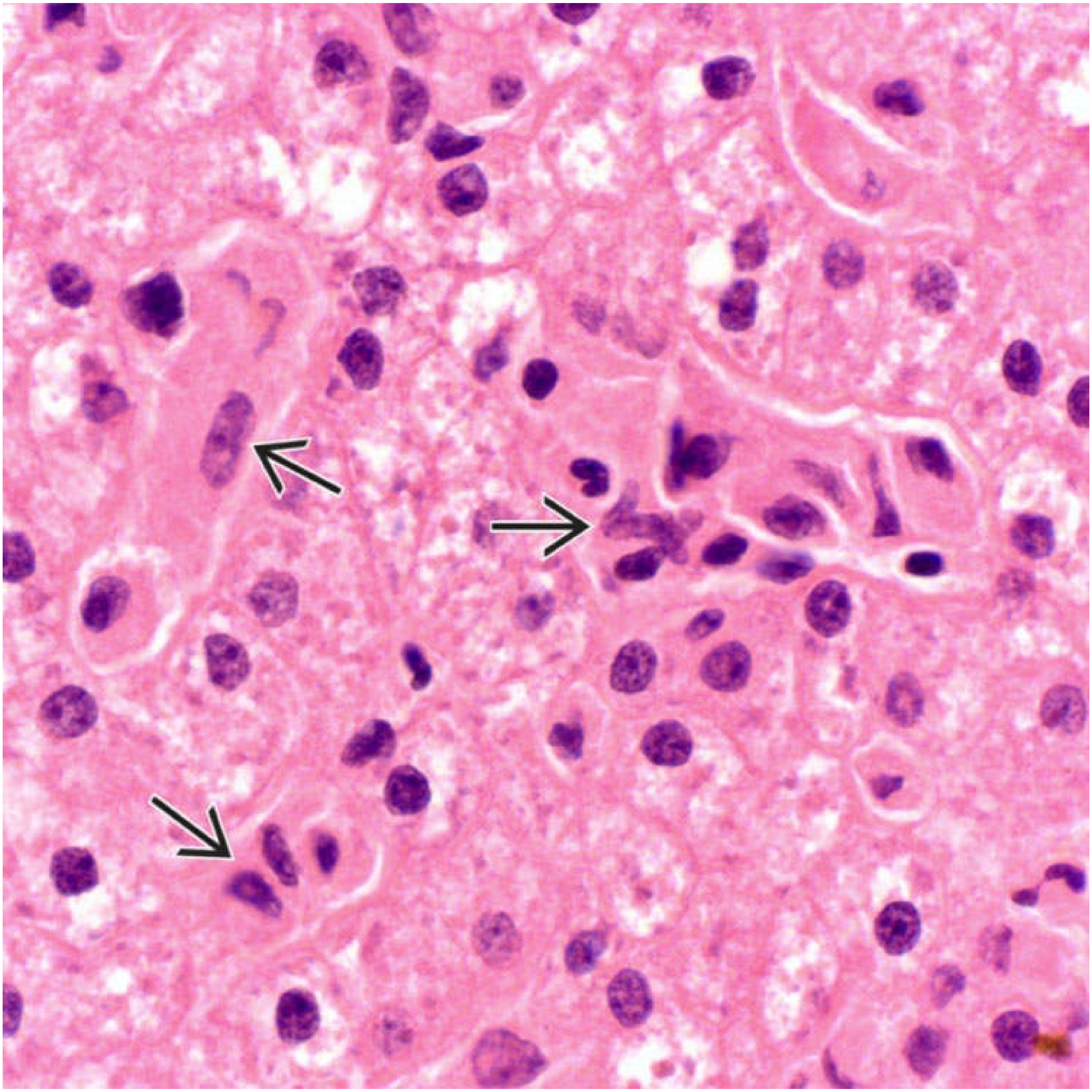
DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Immunostains to exclude LCH are recommended in all clinically &/or histologically diagnosed sclerosing cholangitis cases in children

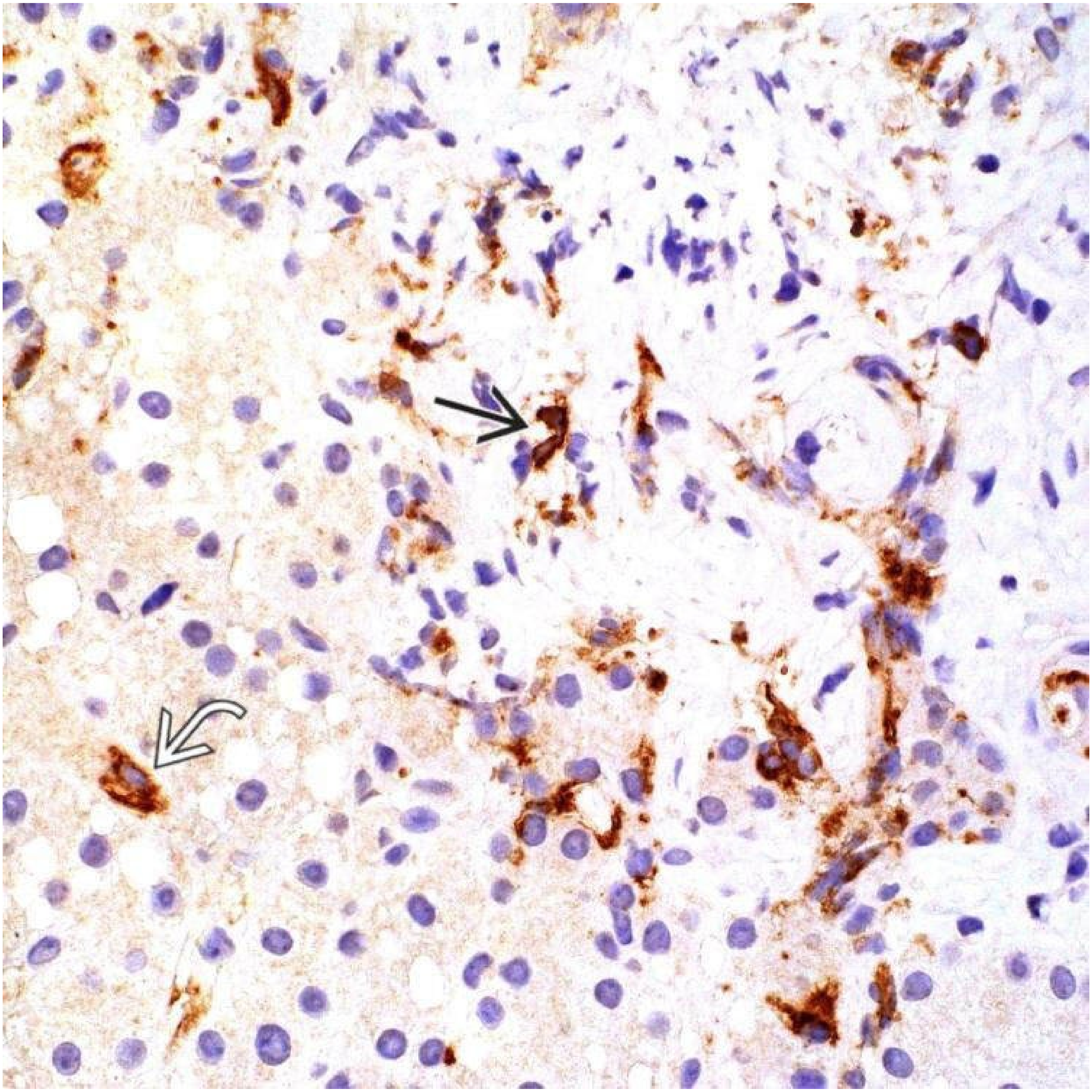


Sinusoidal Infiltration
This hepatic Langerhans cell histiocytosis case shows an extensive infiltration of sinusoids by a mixture of Langerhans cells and non-Langerhans histiocytes.



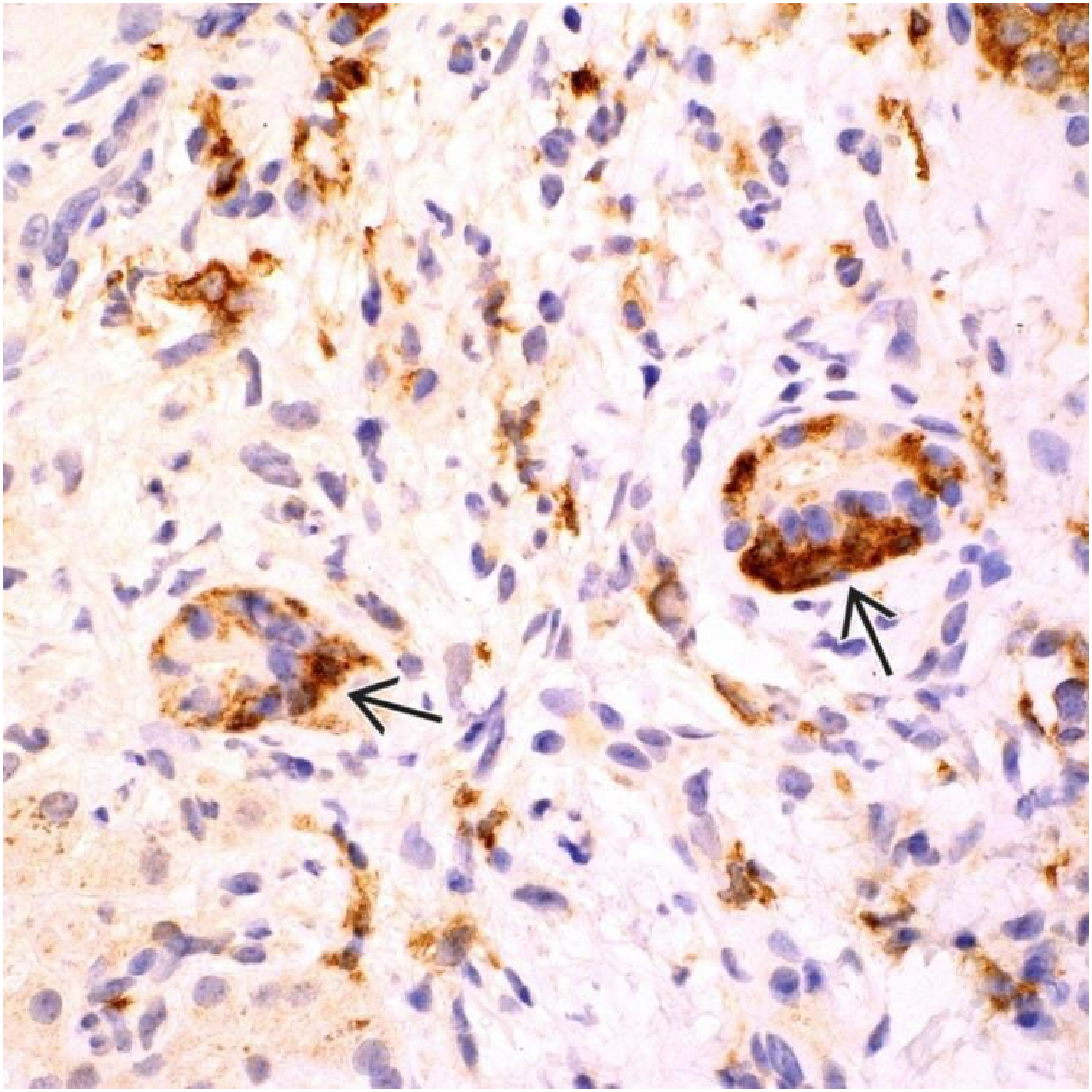
Sinusoidal Infiltration

High-power view of this hepatic Langerhans cell histiocytosis case shows histiocytic cells within sinusoids →, some of which are Langerhans cells. Non-Langerhans histiocytes are also present as part of macrophage activation syndrome.



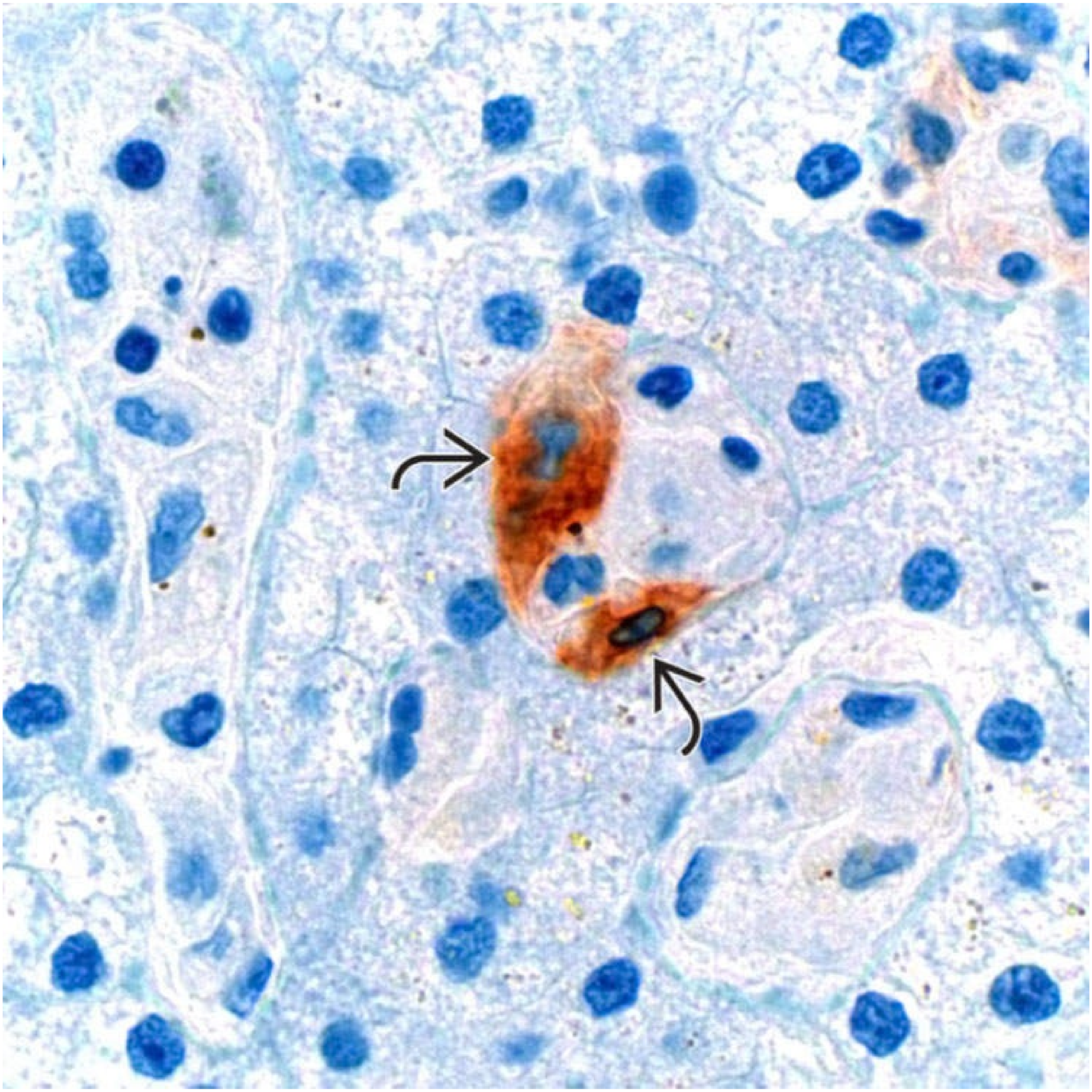
Immunostaining

Immunohistochemical stain for CD1a highlights Langerhans cells mostly in portal tracts →. Scattered Langerhans cells are also present in the lobules ⇗. Similar results are also seen with antibodies to S100 and langerin.



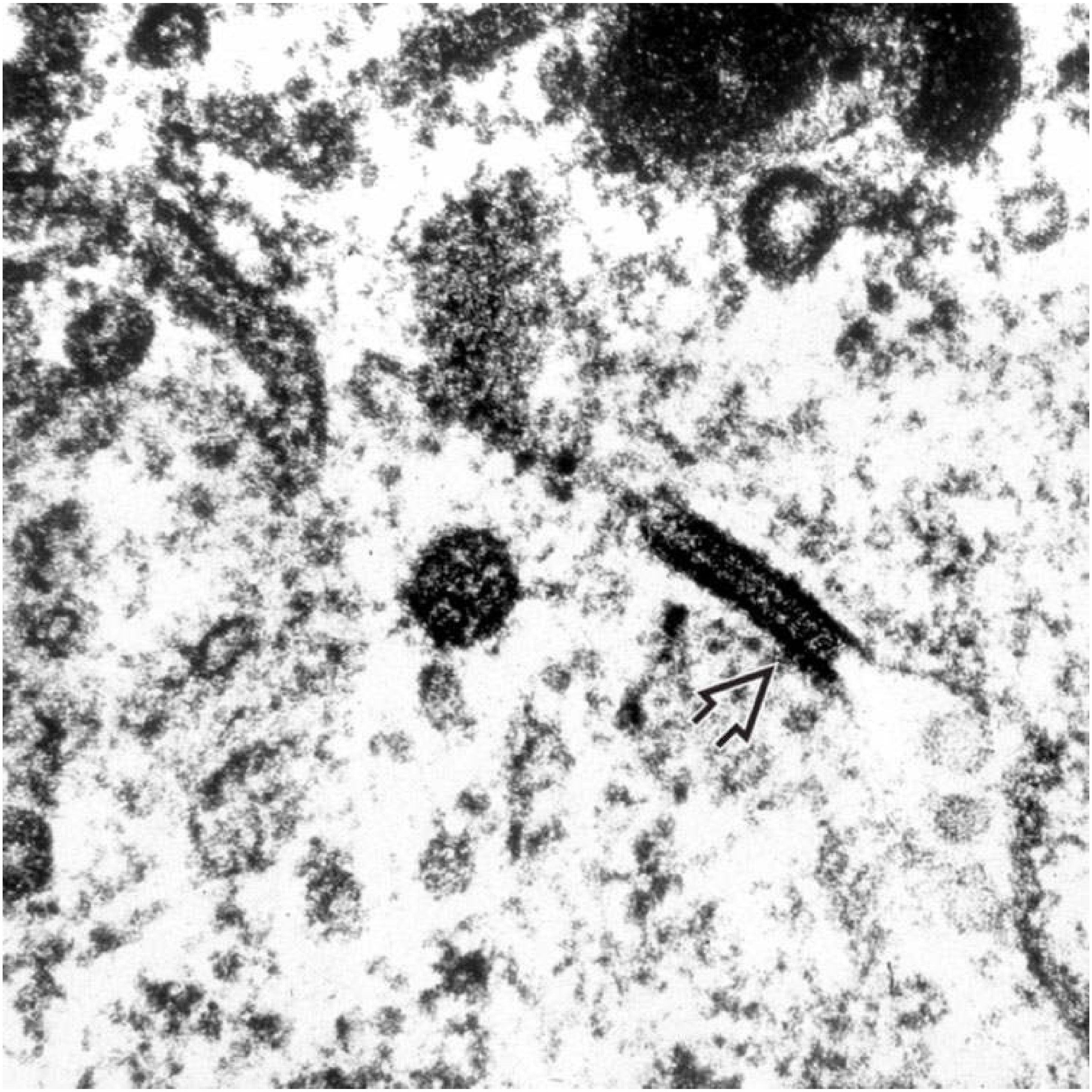
Bile Ducts

Bile duct injury by Langerhans cell infiltration is a characteristic finding of hepatic Langerhans cell histiocytosis. This microphotograph shows Langerhans cells infiltrating the space between epithelial cells and basement membrane as highlighted by CD1a immunostaining →.



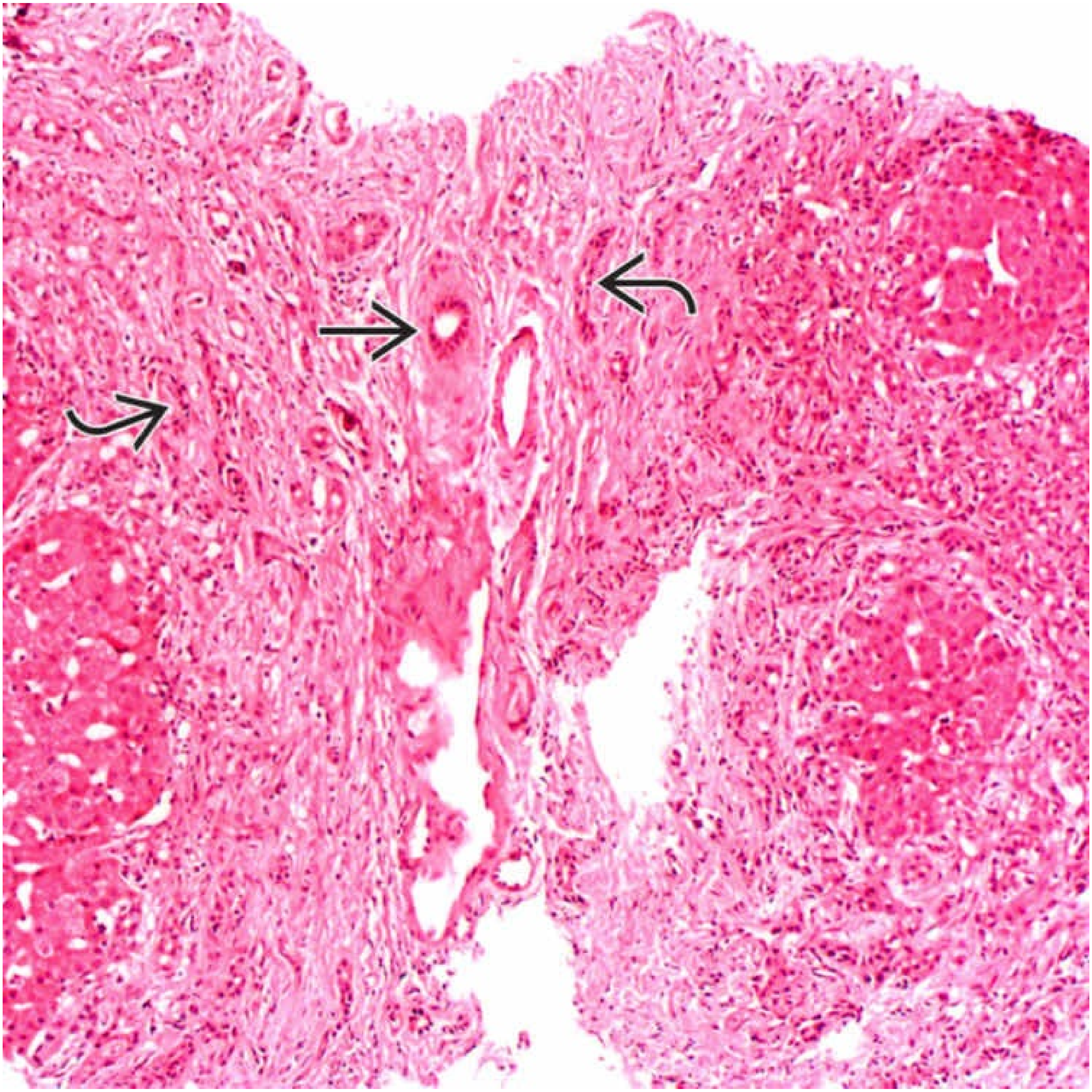
Langerhans Cells in Sinusoids

CD1a immunostaining highlights 2 Langerhans cells ↷ within sinusoids in this case of hepatic Langerhans cell histiocytosis. More Langerhans cells are present in portal tracts (not shown in this field).



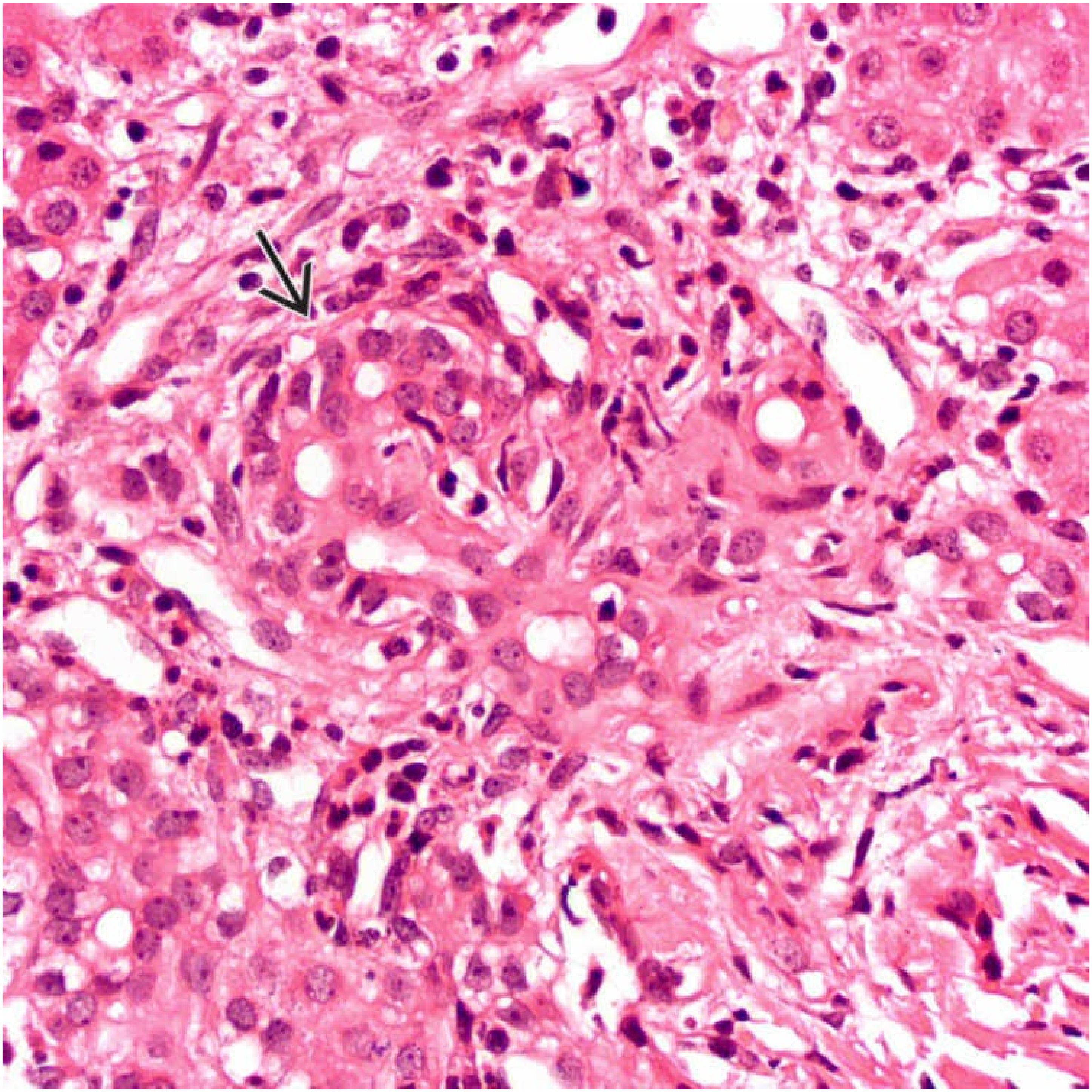
Birbeck Granule

Transmission electron microscopy demonstrates a Birbeck granule ⇨, which is a trilamellar, striated, tennis racket-shaped structure in the cytoplasm of Langerhans cells.

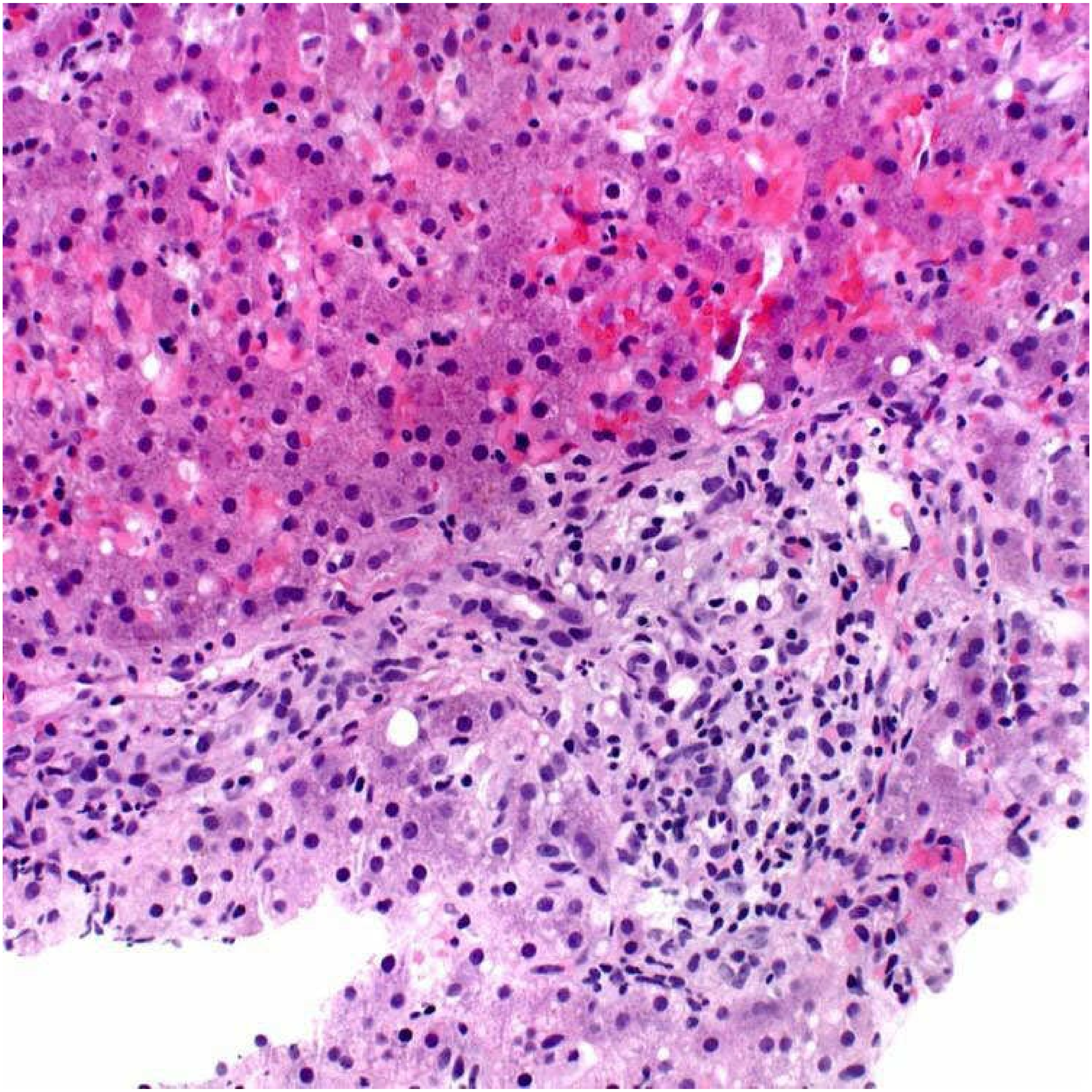


Bridging Fibrosis

This liver biopsy from a child with Langerhans cell histiocytosis shows bridging fibrosis with broad fibrous septa and ductular reaction ↱. The native bile duct is noted in the center of fibrous septum in this microphotograph →.

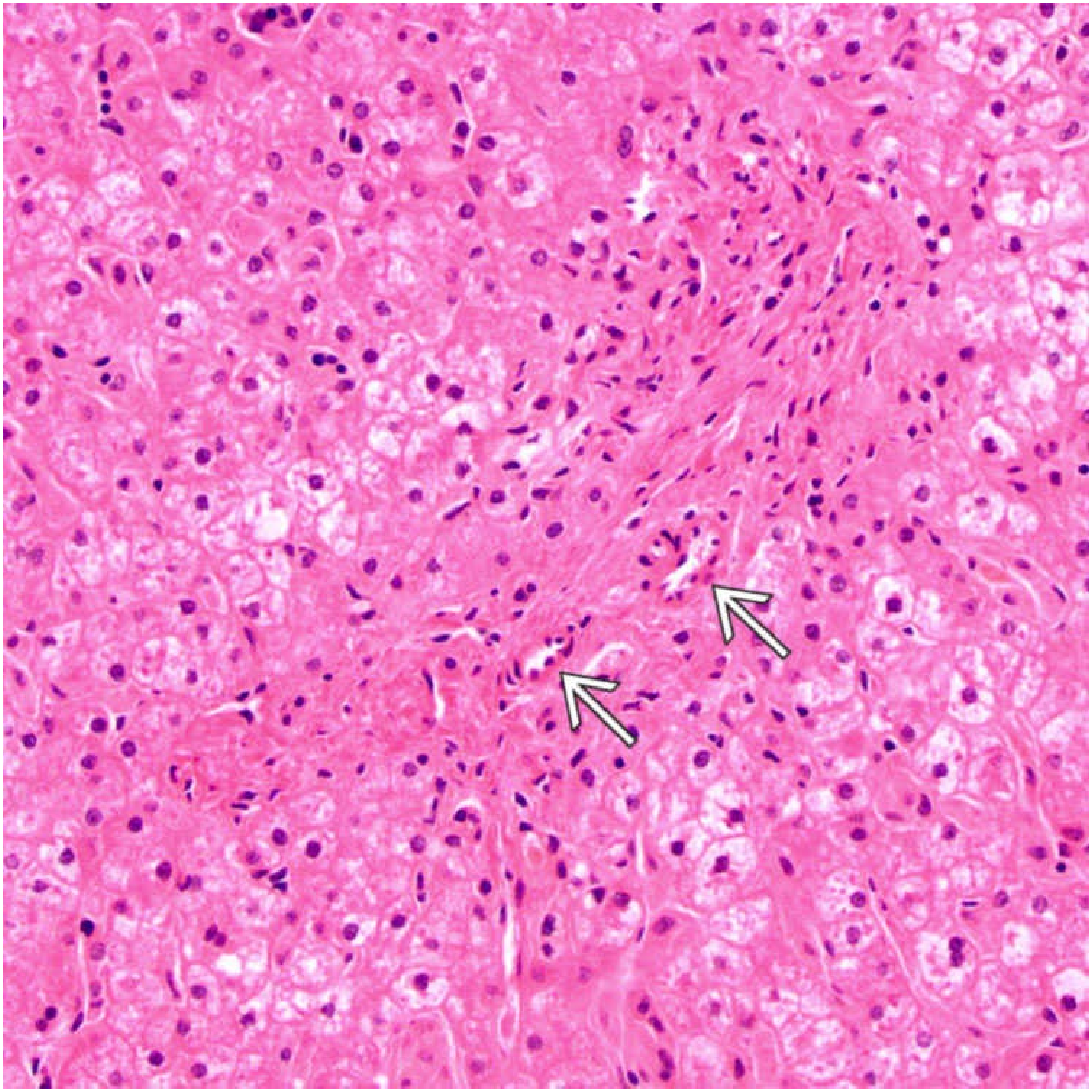


Ductular Reaction
Closer view of the biopsy shows prominent ductular reaction →. Mild mixed inflammatory cell infiltrates are present in portal tracts. These findings are consistent with sclerosing cholangitis secondary to Langerhans cell histiocytosis.



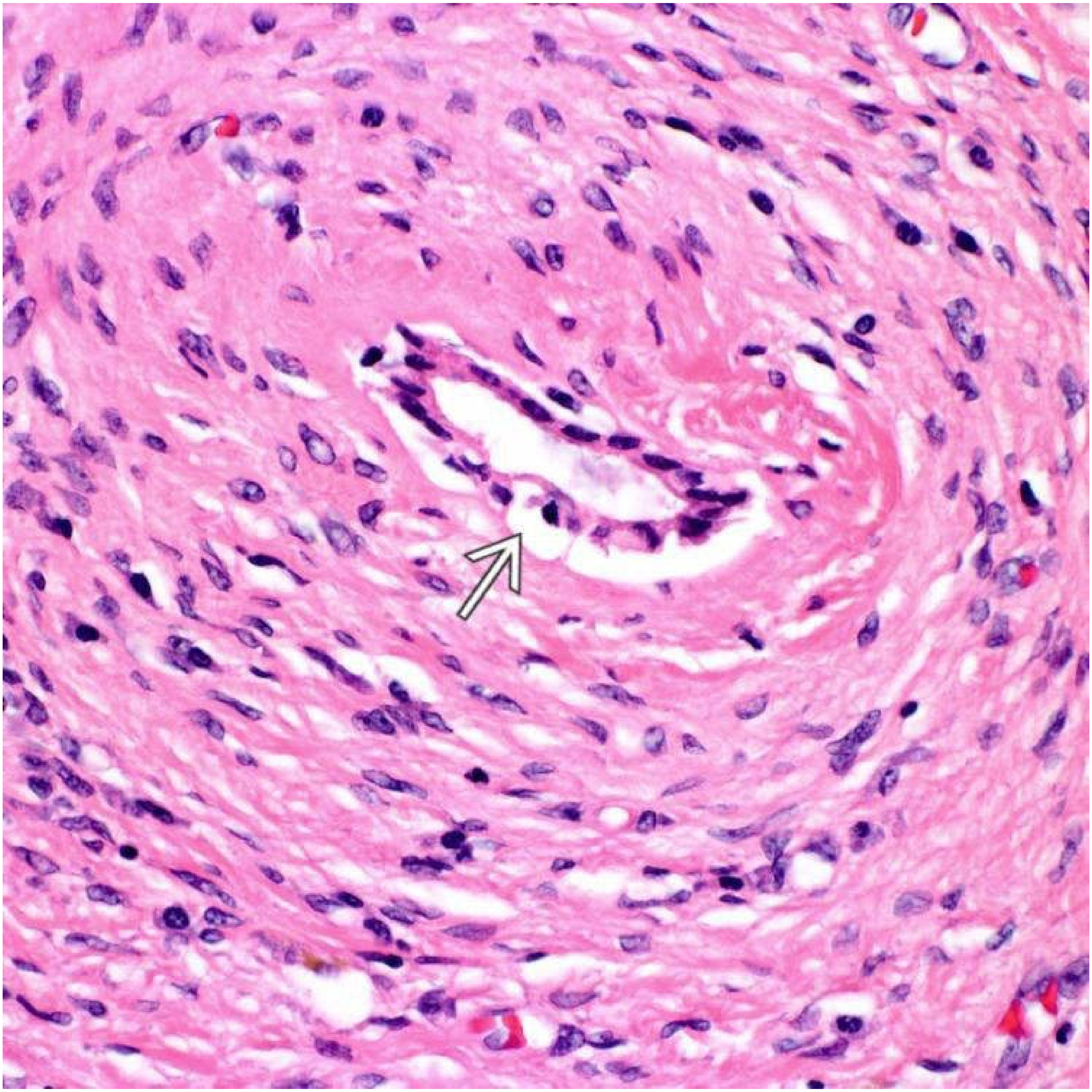
Portal Inflammation

This liver biopsy from a child with multisystem Langerhans cell histiocytosis shows mild mixed inflammatory cell infiltrates in portal tracts. Langerhans cells are not evident histologically but demonstrated by immunostains.

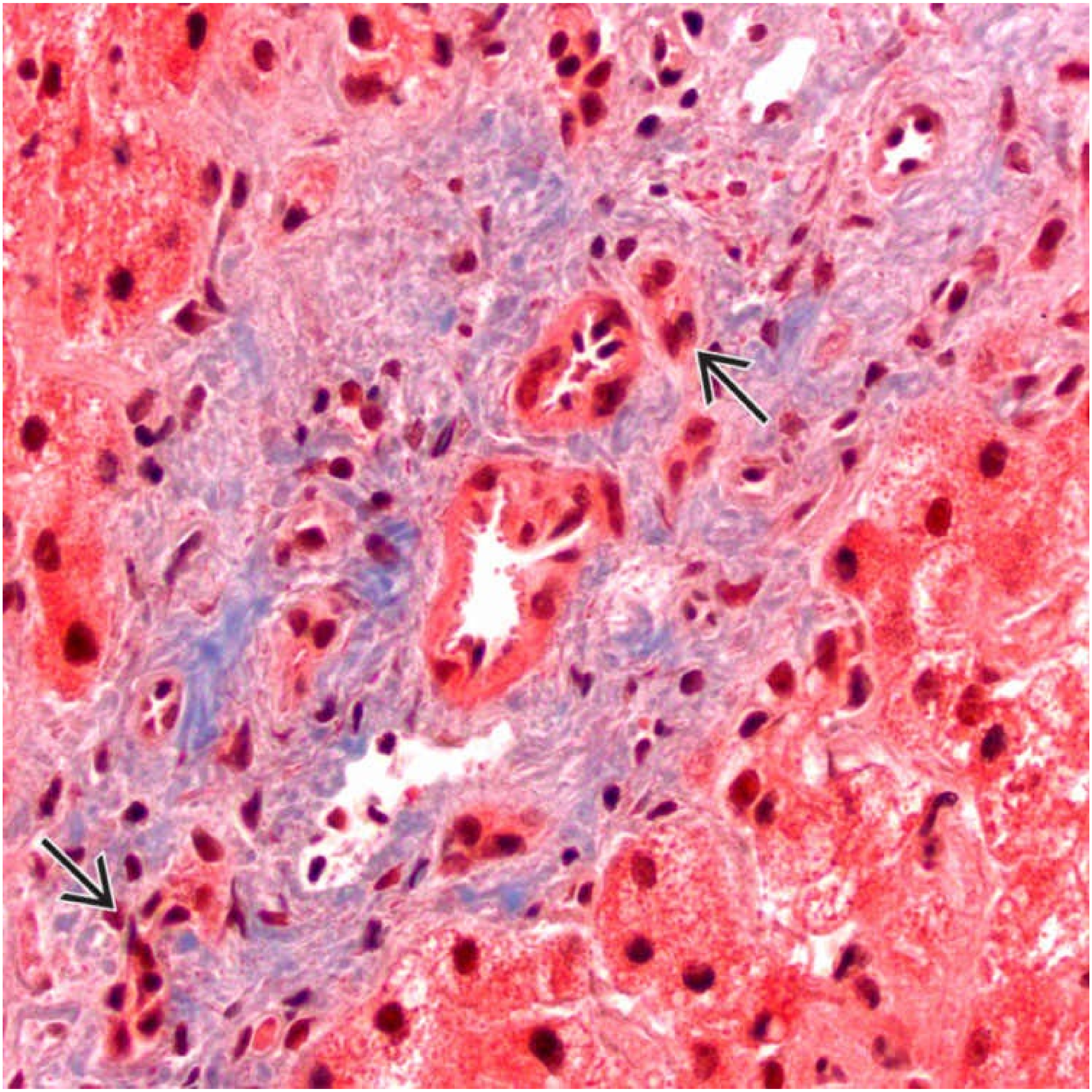


Bile Duct Loss

A liver biopsy from a child with Langerhans cell histiocytosis and cholangiographic evidence of sclerosing cholangitis shows mild portal fibrosis. Note the absence of bile duct in this portal tract. Hepatic artery branches are present ⇒ .



Periduct Concentric Fibrosis
Sclerosing cholangitis secondary to Langerhans cell histiocytosis resembles primary sclerosing cholangitis histologically. Note a degenerating bile duct ⇒ compressed by periduct concentric fibrosis.



Bile Duct Injury
This case of hepatic Langerhans cell histiocytosis with secondary sclerosing cholangitis shows portal fibrosis and small remnants of bile ducts →. Periduct concentric fibrosis is not evident in this portal tract.

SELECTED REFERENCES

1. Berres, ML, et al. Progress in understanding the pathogenesis of Langerhans cell histiocytosis: back to Histiocytosis X? *Br J Haematol*. 2015; 169(1):3–13.
2. Harmon, CM, et al. Langerhans cell histiocytosis: a clinicopathologic review and molecular pathogenetic update. *Arch Pathol Lab Med*. 2015; 139(10):1211–1214.
3. Kaplan, KJ, et al. Liver involvement in Langerhans' cell histiocytosis: a study of nine cases. *Mod Pathol*. 1999; 12(4):370–378.

Hemophagocytic Syndromes

KEY FACTS

Terminology

- Proliferation and activation of macrophages with hemophagocytosis in reticuloendothelial system

Etiology/Pathogenesis

- Familial or primary hemophagocytic syndrome (FHL)
  - Autosomal recessive inheritance
  - 1 in 50,000 live births
- Reactive hemophagocytic syndrome (secondary HLH)
  - Infections, malignancies, autoimmune diseases
- Hyperproduction of cytokines and chemokines due to T-cell dysregulation that causes “cytokine storm” with proliferation and activation of macrophages

Clinical Issues

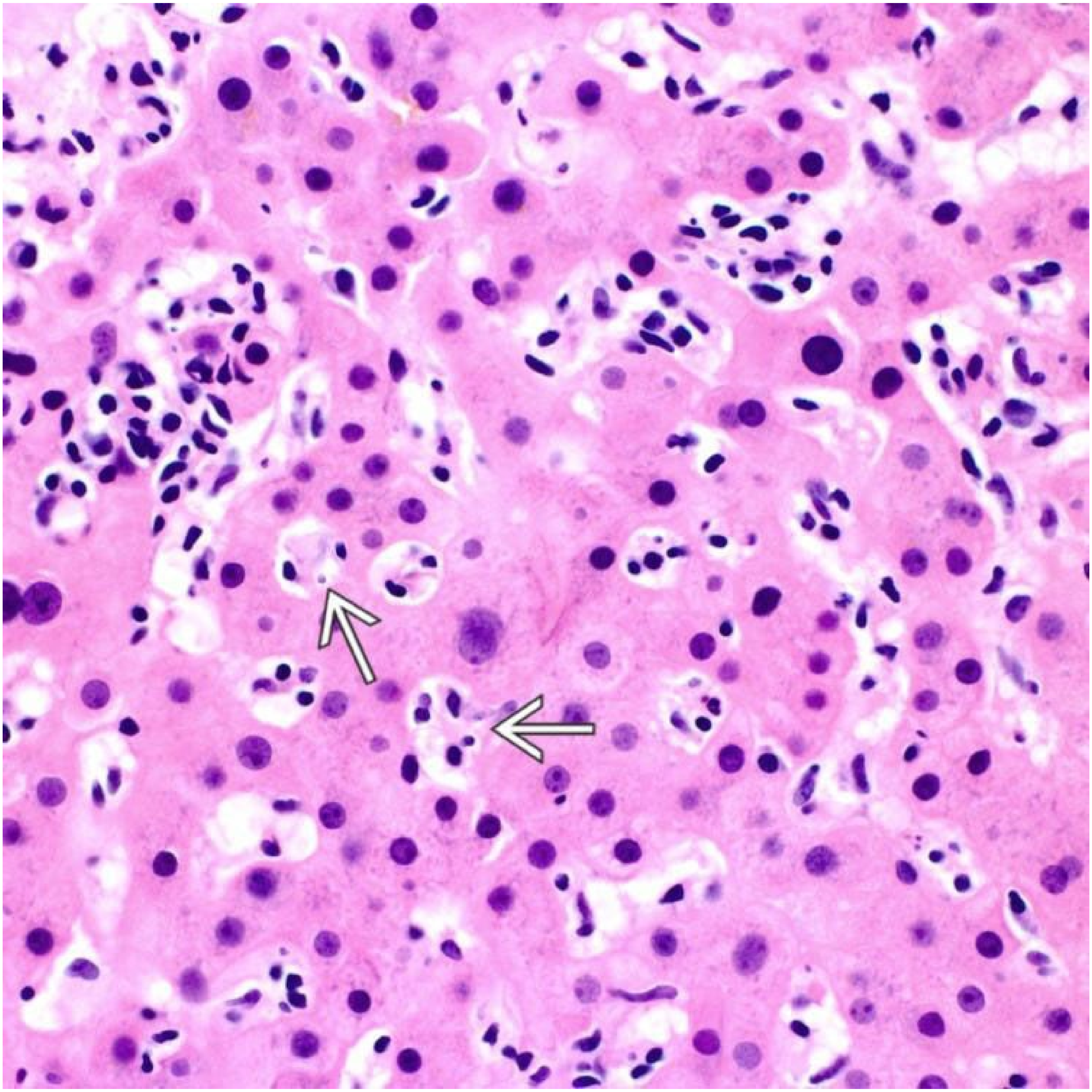
- Presentation
  - FHL typically seen in infants and young children
  - Secondary HLH typically seen in adolescents and adults
- Laboratory tests
  - Hypertriglyceridemia, hyperferritinemia, hypofibrinogenemia
  - Cytopenia affecting ≥ 2 of 3 lineages in peripheral blood
  - Abnormal liver tests
- Prognosis
  - FHL invariably fatal if untreated, with median survival of 2-6 months after diagnosis
  - Varied outcomes for secondary HLH, but full recovery can be achieved

Microscopic

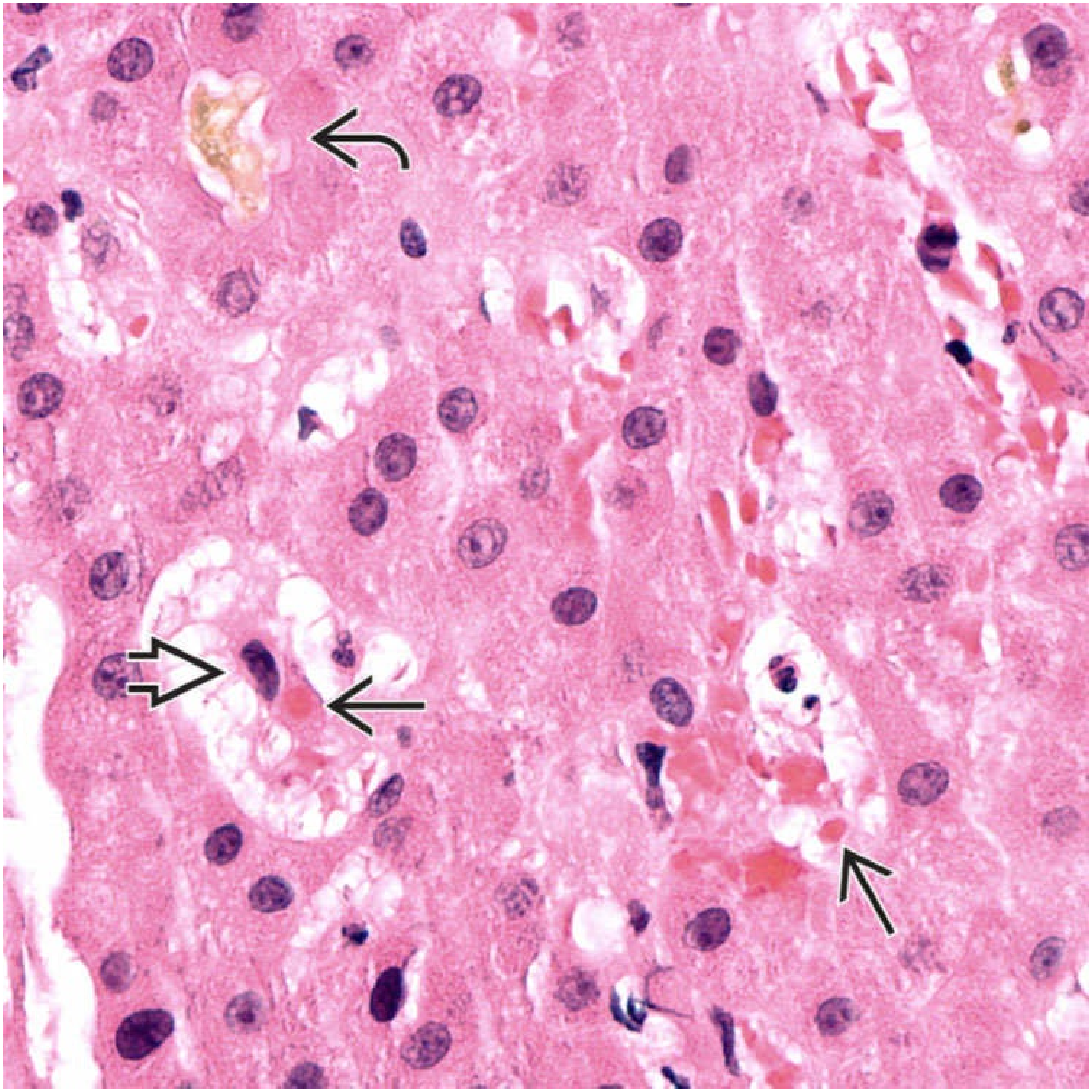
- Kupffer cell hyperplasia and hypertrophy
  - Cytoplasmic engulfment of erythrocytes, leukocytes, and platelets, as well as cell fragments
- Features of underlying diseases, such as EBV hepatitis

Ancillary Tests

- Bone marrow biopsy and aspirate
- Molecular genetic testing for FHL

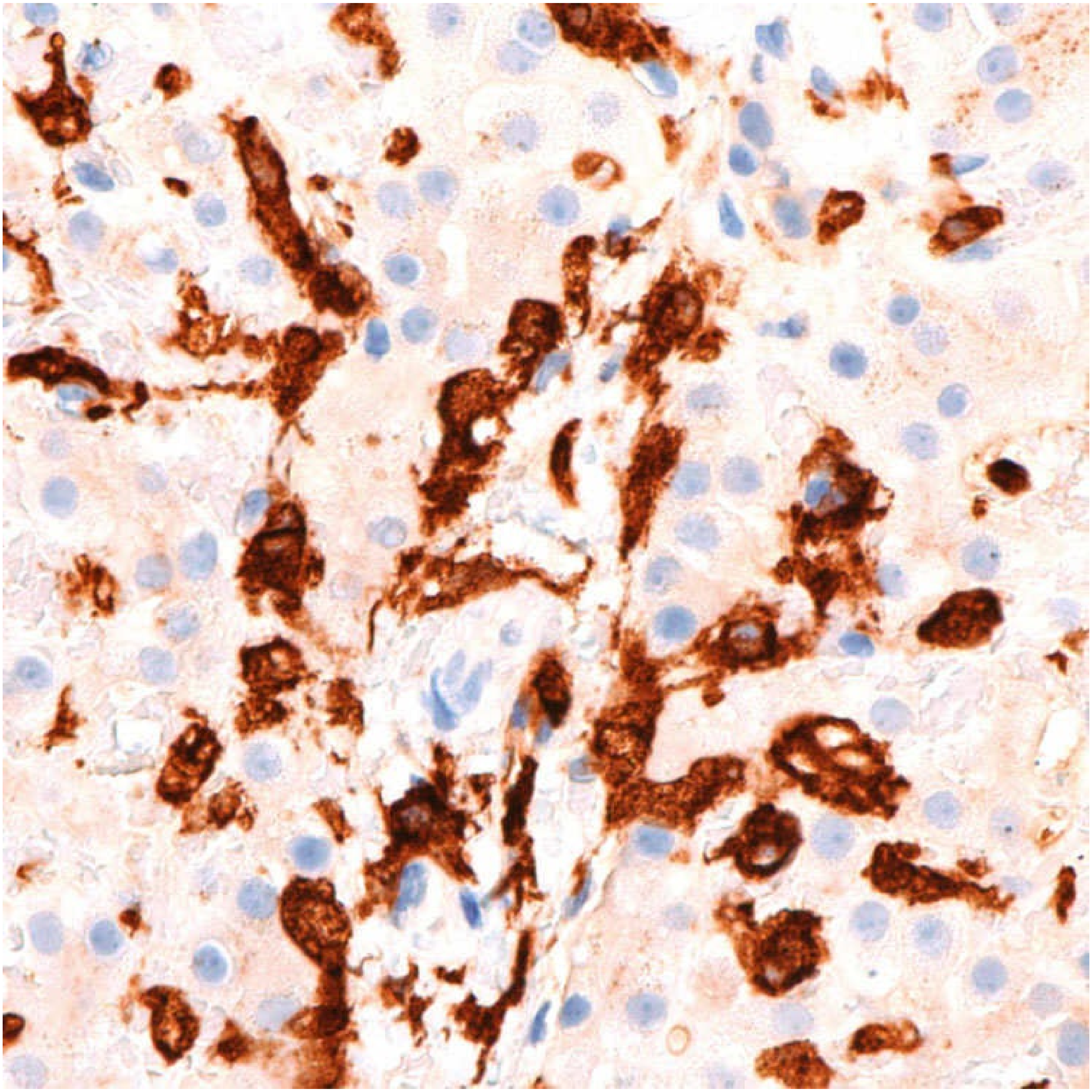


Hemophagocytosis
This liver biopsy shows sinusoidal dilatation with prominent Kupffer cells ⇨. Many Kupffer cells have abundant cytoplasm that contain engulfed lymphocytes. In situ hybridization is positive for EBV RNA in scattered lymphocytes, confirming a diagnosis of EBV hepatitis.

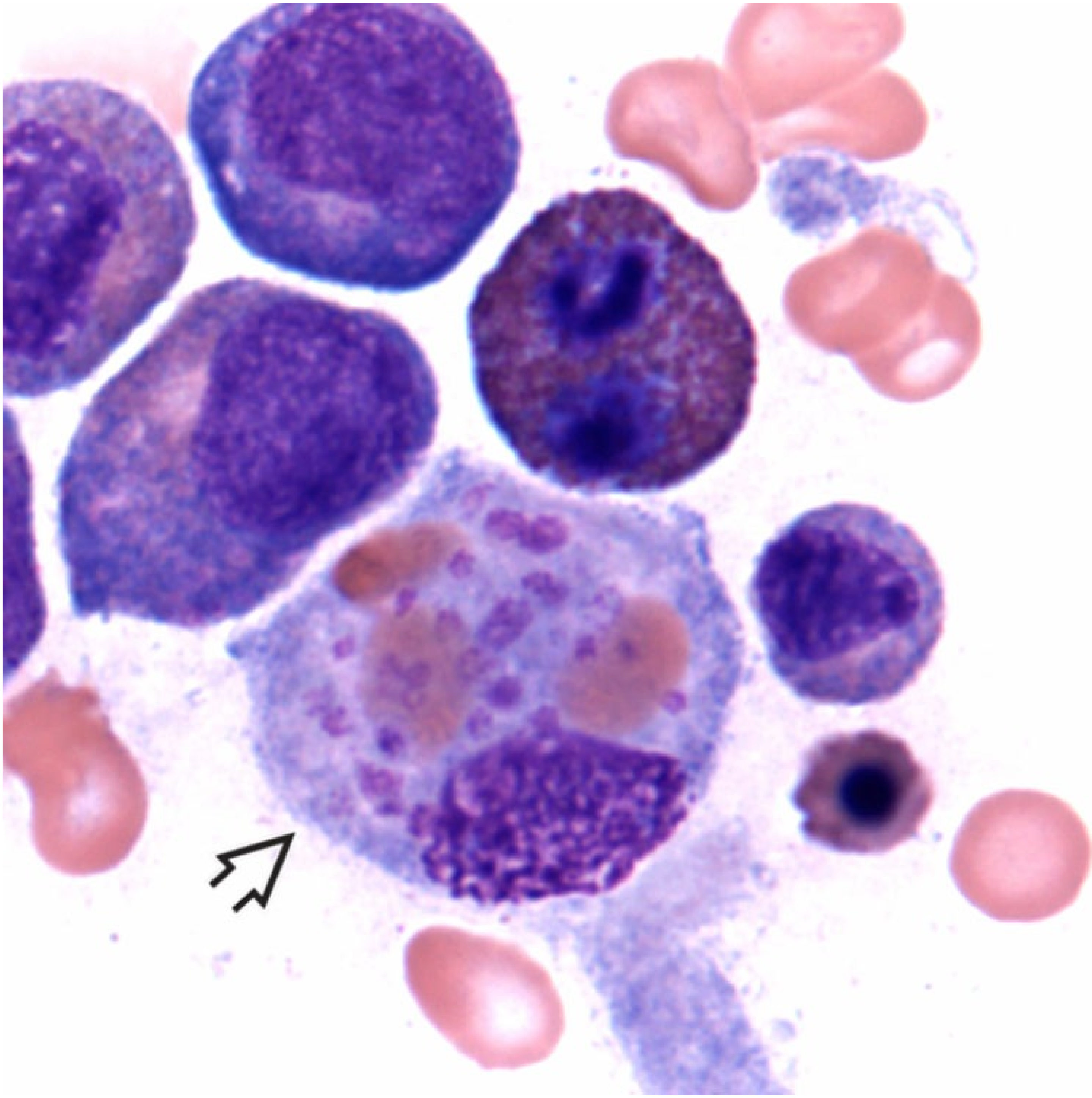


Hemophagocytosis

Hypertrophic Kupffer cells ⇨ in dilated sinusoids contain engulfed red cells in the cytoplasm →, which can be easily overlooked. Focal cholestasis ↷ is noted in this case.



CD163 Immunostain
Immunohistochemical stains using histiocytic markers, such as CD163, can highlight hyperplastic and hypertrophic Kupffer cells, but the stains do not help in the recognition of hemophagocytosis.



Bone Marrow Aspirate
Compared to that in liver biopsy, hemophagocytosis is easier to recognize on a Wright-Giemsa bone marrow smear, which shows a macrophage ➩ containing phagocytosed red cells, platelets, and leukocyte debris.

TERMINOLOGY

Abbreviations

- Hemophagocytic lymphohistiocytosis (HLH), familial HLH (FHL2)

Synonyms

- Hemophagocytic syndrome

Definitions

- Proliferation and activation of macrophages with hemophagocytosis in reticuloendothelial system

ETIOLOGY/PATHOGENESIS

Primary or Familial HLH

- Autosomal recessive inheritance
  - 5 subtypes based on causative genes
  - FHL1: Mutations in unknown gene(s) at chromosome 9q21.3-q22
  - FHL2: Mutations in *PRF1* gene (encoding perforin)
  - FHL3: Mutations in *UNC13D* gene
  - FHL4: Mutations in *STX11* gene
  - FHL5: mutations in *STXBP2* (*UNC18B*) gene

Secondary or Reactive HLH

- Infections
  - Viruses (EBV, HIV, other herpes viruses, etc.)
  - Bacteria
  - Fungi
  - Parasites
- Malignancies
  - Lymphomas/leukemias
  - Carcinomas
- Autoimmune diseases
  - Rheumatologic disorders

Pathogenesis

- T-cell dysregulation
- Hyperproduction of cytokines and chemokines (interferon-γ, TNF-α, IL-1, IL-6, etc.) that causes "cytokine storm"
- Proliferation and activation of macrophages

CLINICAL ISSUES

Epidemiology

- Incidence
  - 1 in 50,000 live births for FHL
  - Unknown for secondary HLH
- Age
  - Typically seen in infants and young children for FHL
  - Typically seen in adolescents and adults for secondary HLH

Presentation

- Persistent fever
- Splenomegaly, hepatomegaly, lymphadenopathy
- Easy bruisability, jaundice, skin rash
- Neurologic abnormalities

Laboratory Tests

- Cytopenia affecting ≥ 2 of 3 lineages in peripheral blood
- Hypertriglyceridemia
- Hypofibrinogenemia
- Hyperferritinemia
- Low or absent natural killer cell activity
- High plasma level of soluble IL-2 receptor
- Abnormal liver functions
- Bone marrow biopsy and aspirate
- Molecular genetic testing for mutations

Treatment

- Combined cytotoxic chemotherapy and immunotherapy
- Antibiotics &/or antiviral agents
- Hematopoietic stem cell transplantation
- Treatment of underlying diseases

Prognosis

- Invariably fatal for FHL if untreated, with median survival of 2-6 months after diagnosis
- Varied outcomes for secondary HLH, but full recovery can be achieved
- 55% 3-year overall survival rate for all types of HLH treated with 1997 protocol
- 62% 3-year overall survival rate for patients treated with stem cell transplantation

MICROSCOPIC

Histologic Features

- Sinusoidal dilatation
  - Kupffer cell hyperplasia and hypertrophy
  - Cytoplasmic engulfment of erythrocytes, leukocytes, and platelets, as well as cell fragments
  - Stainable iron may be present
- Mild portal lymphohistiocytic infiltrates
- Features of underlying diseases, such as EBV hepatitis

DIFFERENTIAL DIAGNOSIS

FHL vs. Secondary HLH

- Age of onset
- Family history
- Molecular genetic testing

Hepatic Rosai-Dorfman Disease

- Usually seen as multiple small granuloma-like histiocytic aggregates or larger nodules
- Portal and sinusoidal infiltration may be seen
- Characteristic phagocytosis of intact lymphocytes and red cells by large histiocytes (emperipolesis)
- Positive S100 immunostain

Hepatic Involvement by Leukemia or Lymphoma

- Infiltration by monotonous/atypical lymphoid or myeloid cells
- Flow cytometry and immunohistochemistry are helpful

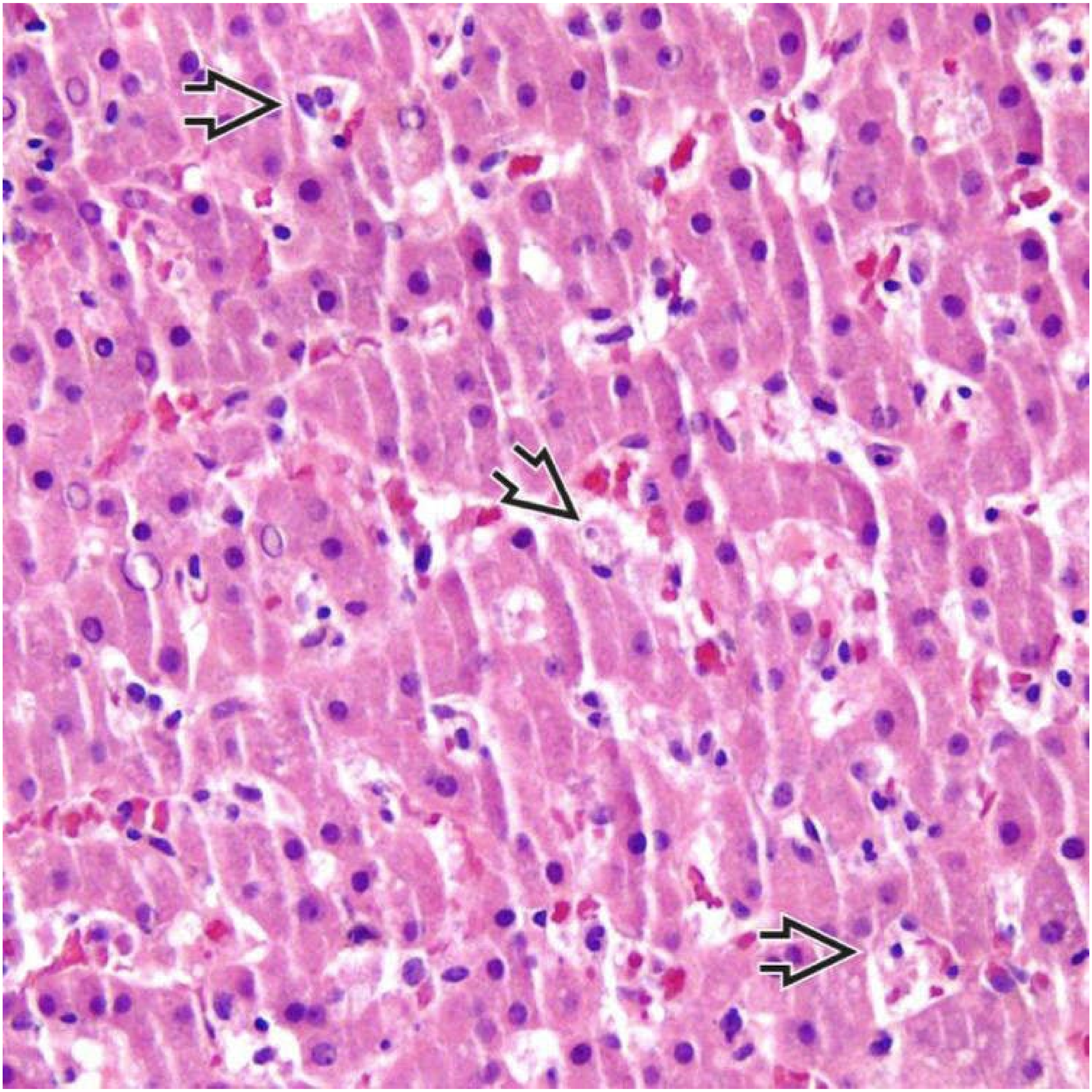
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

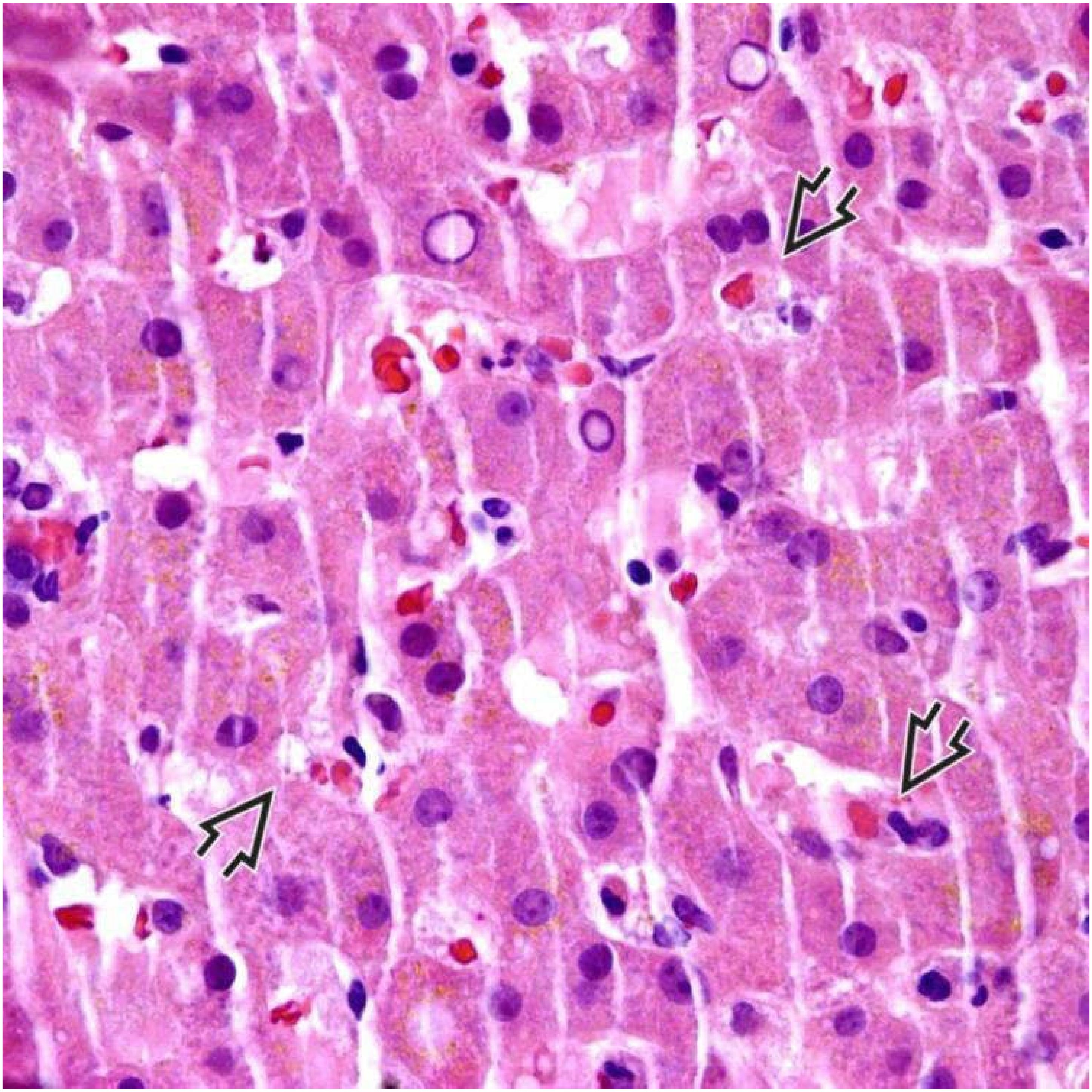
- Abnormal activation of benign macrophages by genetic or reactive mechanisms

Pathologic Interpretation Pearls

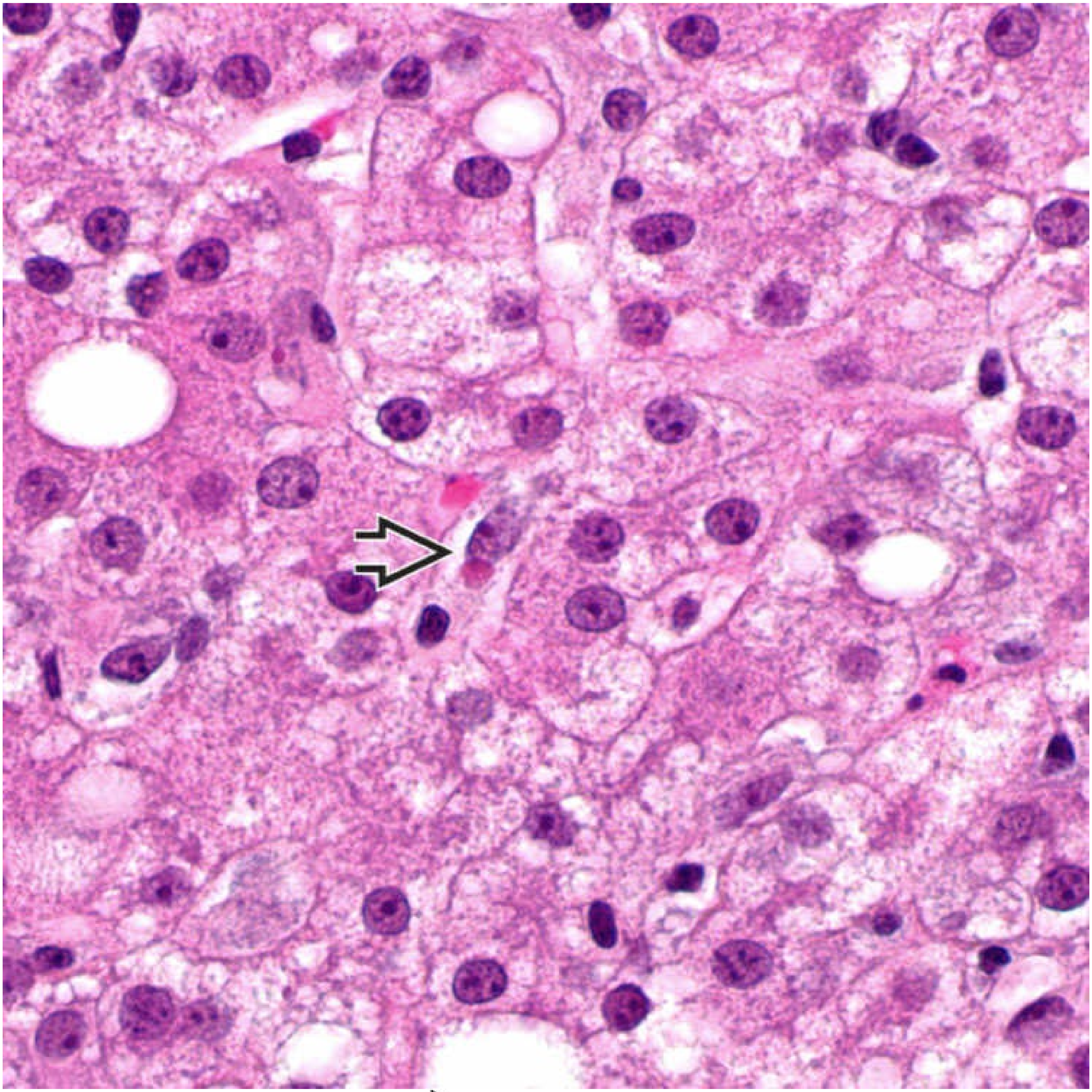
- Kupffer cell hyperplasia with phagocytosed hematopoietic cells, which can be easily overlooked



At low power, a clue to hemophagocytosis is often increased numbers of Kupffer cells, which are often enlarged ➩. The sinusoids are dilated to accommodate them.



This high-power micrograph shows numerous enlarged Kupffer cells containing phagocytosed red blood cells ➪ .



Erythrophagocytosis by a Kupffer cell ➪ is seen in a case of EBV-induced infectious mononucleosis.

SELECTED REFERENCES

1. Brisse, E, et al. Advances in the pathogenesis of primary and secondary haemophagocytic lymphohistiocytosis: differences and similarities. *Br J Haematol*. 2016. [ePub].
2. Madkaikar, M, et al. Current Updates on Classification, Diagnosis and Treatment of Hemophagocytic Lymphohistiocytosis (HLH). *Indian J Pediatr*. 2016; 83(5):434–443.
3. Morimoto, A, et al. Hemophagocytic lymphohistiocytosis: pathogenesis, diagnosis, and management. *Pediatr Int*. 2016. [ePub].

4. Zhang, L, et al. Hereditary and acquired hemophagocytic lymphohistiocytosis. *Cancer Control*. 2014; 21(4):301–312.

PART II
Pancreas and Biliary Tract

OUTLINE

SECTION 1
DEVELOPMENTAL/CONGENITAL

OUTLINE

Congenital Pancreatic Cyst

KEY FACTS

Etiology/Pathogenesis

- Developmental anomaly of pancreatic ductal system
  - Presumably due to failure of embryonic pancreatic ducts to regress, when they are replaced by permanent ones, that leads to their obstruction and cyst formation in utero
  - May be associated with other congenital anomalies, such as von Hippel-Lindau disease, polycystic kidney disease, etc.

Clinical Issues

- Exceedingly rare
- May be found at any age but usually in children younger than 2 years
- Often incidental finding, but may show signs and symptoms of GI or biliary obstruction or pancreatitis due to pressure on adjacent organs
- Any location within pancreas but more common in body or tail

Macroscopic

- Usually single, unilocular, thin-walled cystic lesion
  - Typically 1-2 cm in size but can be larger
- Can be multiple, multilocular
  - May diffusely involve entire pancreas
  - More common in patients with von Hippel-Lindau or polycystic kidney disease
- Does not communicate with pancreatic ductal system

Microscopic

- Cysts are lined by single layer of nonmucin-producing epithelium that can be flattened, cuboidal to columnar
- Fibrous or fibroinflammatory cyst wall

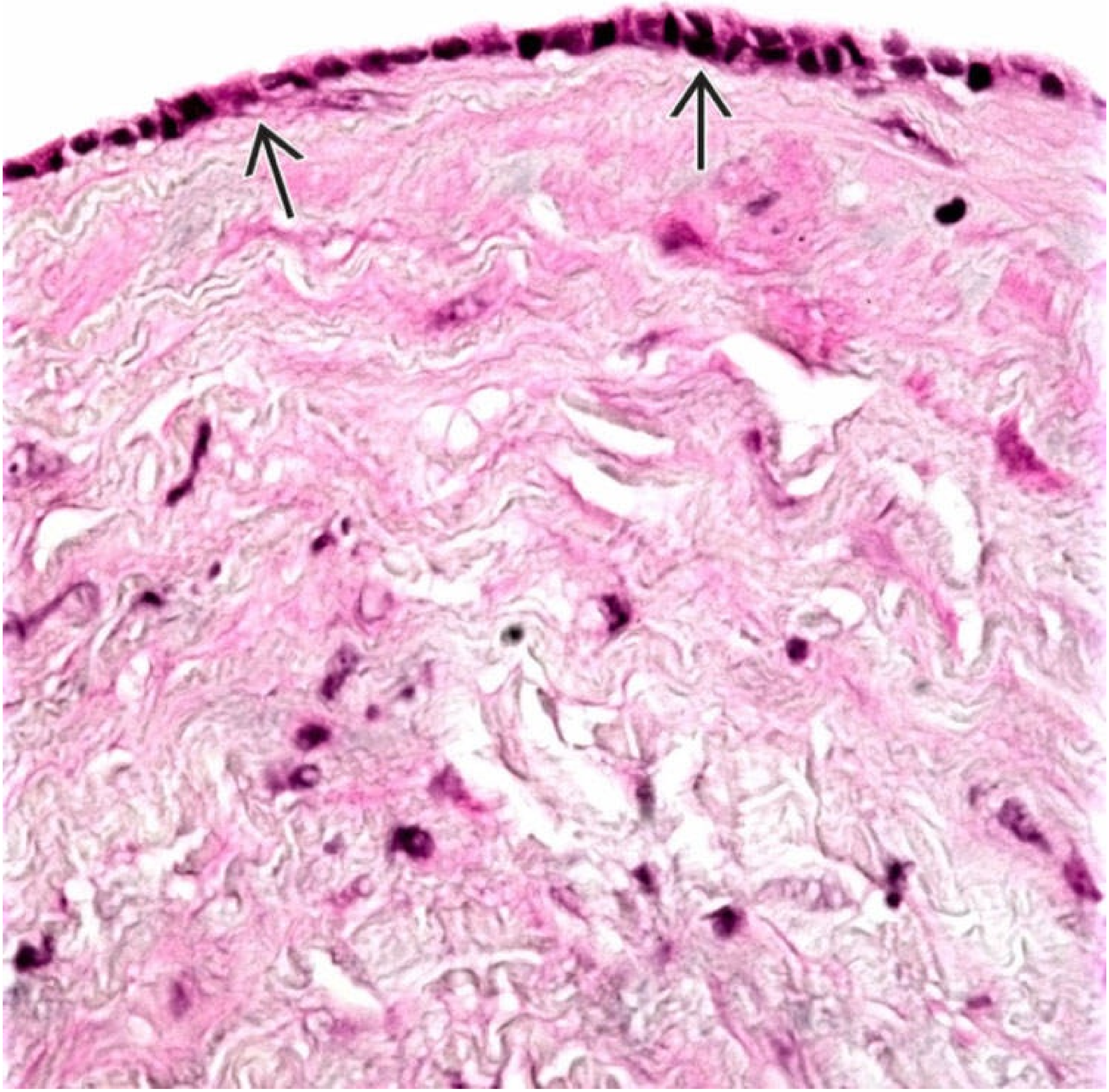
Top Differential Diagnoses

- Enteric duplication cyst
- Retention cyst
- Pseudocyst
- Serous cystadenoma

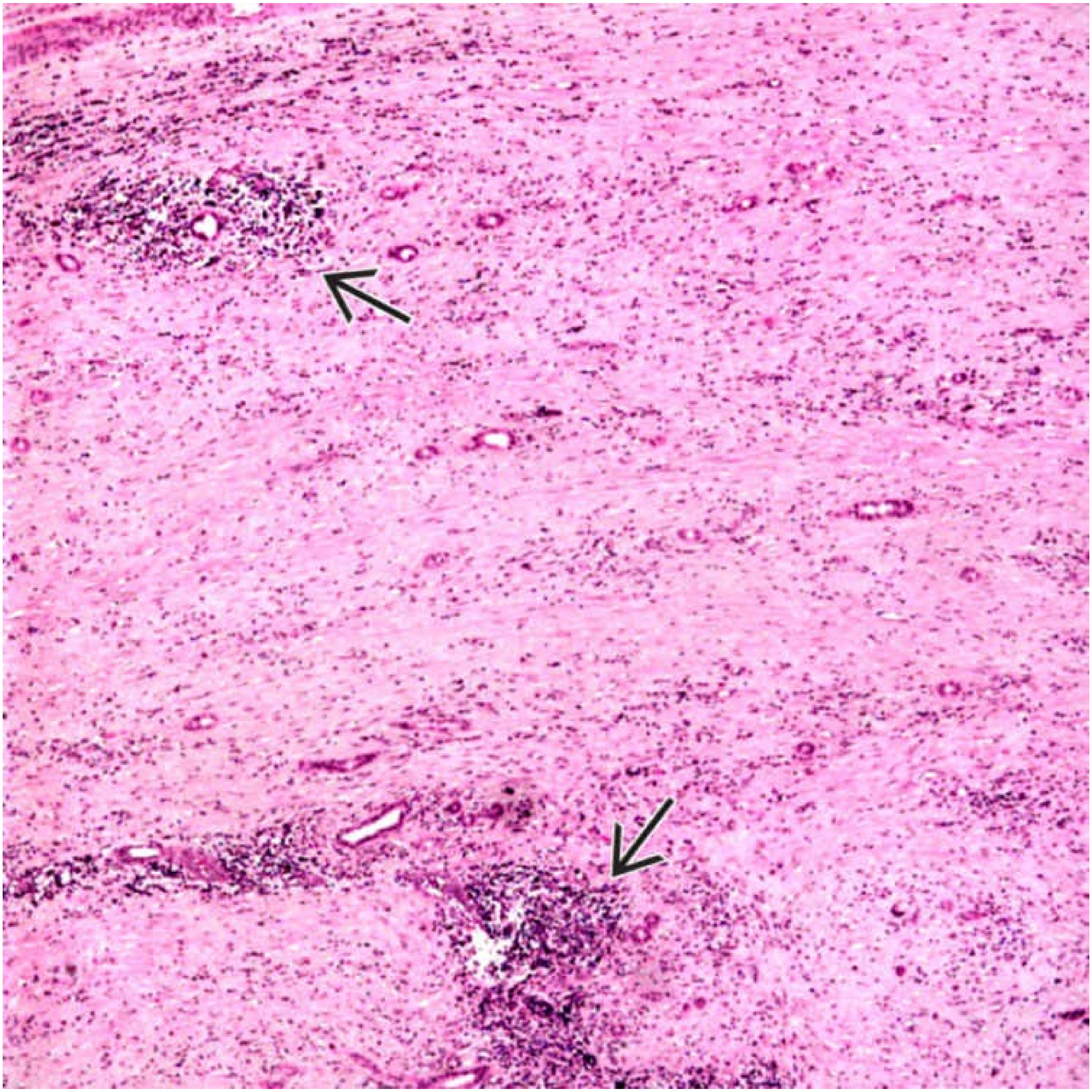
Unilocular Cyst

The enlarged pancreatic head mass was bisected to reveal a unilocular cyst ⇒ that did not communicate with the pancreatic duct. The thin fibrous cyst wall is smooth with focal areas of hemorrhage.

Flattened Epithelial Lining
This low-power view of a congenital pancreatic cyst shows a unilocular cyst lined by a single layer of attenuated epithelium →. The cyst wall is fibrotic.



Epithelial Lining
The cystic space in a congenital pancreatic cyst is typically lined by a single layer of flattened, cuboidal or columnar nonmucinous epithelium →, similar to that seen in benign pancreatic ducts.



Cyst Wall
The wall of a congenital pancreatic cyst typically shows fibrosis and may contain varying degrees of inflammation consisting mainly of lymphocytes →.

TERMINOLOGY

Synonyms

• Dysgenetic cyst

Definitions

• Rare, benign, congenital, epithelial-lined intrapancreatic cyst that does not communicate with ductal

system

ETIOLOGY/PATHOGENESIS

Developmental Anomaly

- Developmental anomaly of pancreatic ductal system
  - Presumably due to failure of embryonic pancreatic ducts to regress, when they are replaced by permanent ones, that leads to their obstruction and cyst formation in utero
- May be associated with other congenital anomalies
  - von Hippel-Lindau disease
  - Polycystic kidney disease
  - Oral-facial-digital syndrome type 1
  - Jeune syndrome
  - Meckel-Gruber syndrome
  - Beckwith-Wiedemann syndrome
  - Other congenital anomalies: Anorectal malformation, polydactyly, short-limb dwarfism, renal tubular ectasia

CLINICAL ISSUES

Epidemiology

- Incidence
  - Exceedingly rare
- Age
  - May be found at any age but usually in children younger than 2 years
- Sex
  - Female predominance

Site

- Any location within pancreas but more common in body or tail

Presentation

- Often asymptomatic
  - Usually found incidentally, such as by antenatal ultrasound
- Abdominal mass or distention when cyst is large
  - Signs and symptoms of upper GI or biliary obstruction or pancreatitis due to pressure on adjacent organs

Laboratory Tests

- Cyst fluid shows high amylase levels

Treatment

- Complete cystectomy or distal pancreatectomy for lesions in pancreatic body or tail
- Internal drainage via cystoduodenostomy or Roux-en-Y cystojejunostomy for lesions in pancreatic head

Prognosis

- Good

IMAGING

Radiographic Findings

- Solitary or multiple cystic lesions in pancreas

MACROSCOPIC

General Features

- Usually single, unilocular, thin-walled cystic lesion
  - Typically 1-2 cm in size but can be larger
- Can be multiple or multilocular
  - May diffusely involve entire pancreas
    - More common in patients with von Hippel-Lindau or polycystic kidney disease
- Do not communicate with pancreatic ductal system
- Serous cyst fluid

MICROSCOPIC

Histologic Features

- Cysts are lined by single layer of nonmucin-producing epithelium that can be flattened, cuboidal to columnar
- Fibrous or fibroinflammatory cyst wall

DIFFERENTIAL DIAGNOSIS

Pancreatic Cysts Associated With Hereditary Disorders or Congenital Syndromes

- Entities with multiple pancreatic cysts or polycystic pancreas

Enteric Duplication Cyst

- More common in pancreatic head; may communicate with pancreatic duct
  - Unilocular cyst lined by variety of epithelial cell types surrounded by smooth muscle, recapitulating gut
    - Small intestinal, gastric, squamous, respiratory, or ciliated

Retention Cyst

- Usually seen in context of chronic pancreatitis or mass lesion causing obstruction
- Communicates with ductal system

Pseudocyst

- Consequence of acute or chronic pancreatitis, trauma, or infection
- No epithelial lining

Serous Cystadenoma

- Can be macrocystic or even unilocular
- Lined by single layer of cuboidal to flattened epithelium with clear cytoplasm

Cystic Fibrosis

- Pancreatic cysts are not congenital but develop in 1st few months of life
- Dilatation of acini and ductules with eosinophilic secretions, acinar and lobular atrophy
- Pancreas replaced by adipose tissue

SELECTED REFERENCES

1. Warnock, WT, et al. Congenital cyst of the pancreas: a case report and review of literature. *Fetal Pediatr Pathol*. 2016; 35(4):265–271.
2. Al-Salem, AH, et al. Congenital pancreatic cyst: diagnosis and management. *J Pediatr Gastroenterol Nutr*. 2014; 59(4):e38–e40.
3. Basturk, O, et al. Pancreatic cysts: pathologic classification, differential diagnosis, and clinical implications. *Arch Pathol Lab Med*. 2009; 133(3):423–438.

Cystic Fibrosis, Pancreas

KEY FACTS

Terminology

- Genetic disorder affecting fluid secretion in exocrine glands and epithelial cells lining respiratory, pancreaticobiliary, gastrointestinal, and reproductive tracts

Etiology/Pathogenesis

- Mutations of cystic fibrosis transmembrane conductance regulator (*CFTR*) gene on chromosome 7q31.2
  - Encodes chloride ion channel protein that regulates fluid balance across epithelial cells
  - Most common mutation is ΔF508, seen in 70% of cystic fibrosis (CF) patients
  - Defective chloride transport leads to thick and tenacious fluid secretions
  - – Blockage of exocrine pancreatic ducts
  - – Damage of pancreatic tissue by accumulated digestive enzymes

Clinical Issues

- Most common autosomal recessive disorder in Caucasians, affecting 1:2,000-3,000 newborns
  - Exocrine pancreatic insufficiency occurs in majority (85-90%) of CF patients
  - Pancreas abnormalities can be seen as early as 32- to 38-weeks of gestation and progressively worsen with age
  - Malabsorption due to exocrine pancreatic insufficiency
  - Steatorrhea, deficiency of fat-soluble vitamins, failure to thrive
- Average life expectancy is 37-48 years in developed countries, and continues to increase
  - Lung problems responsible for 80% deaths

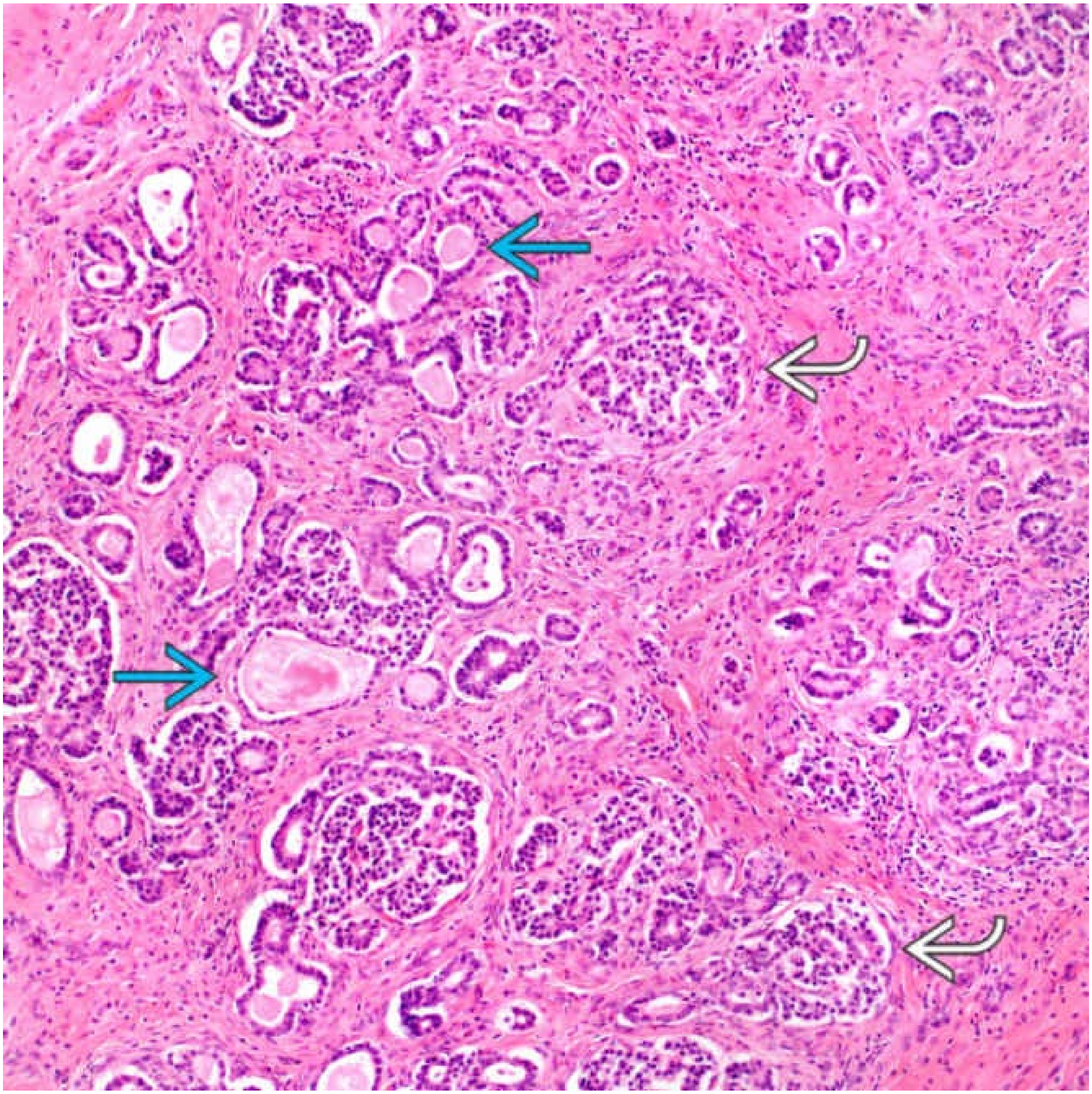
Macroscopic

- Small, firm, and nodular pancreas, often with cystic spaces and fatty replacement

Microscopic

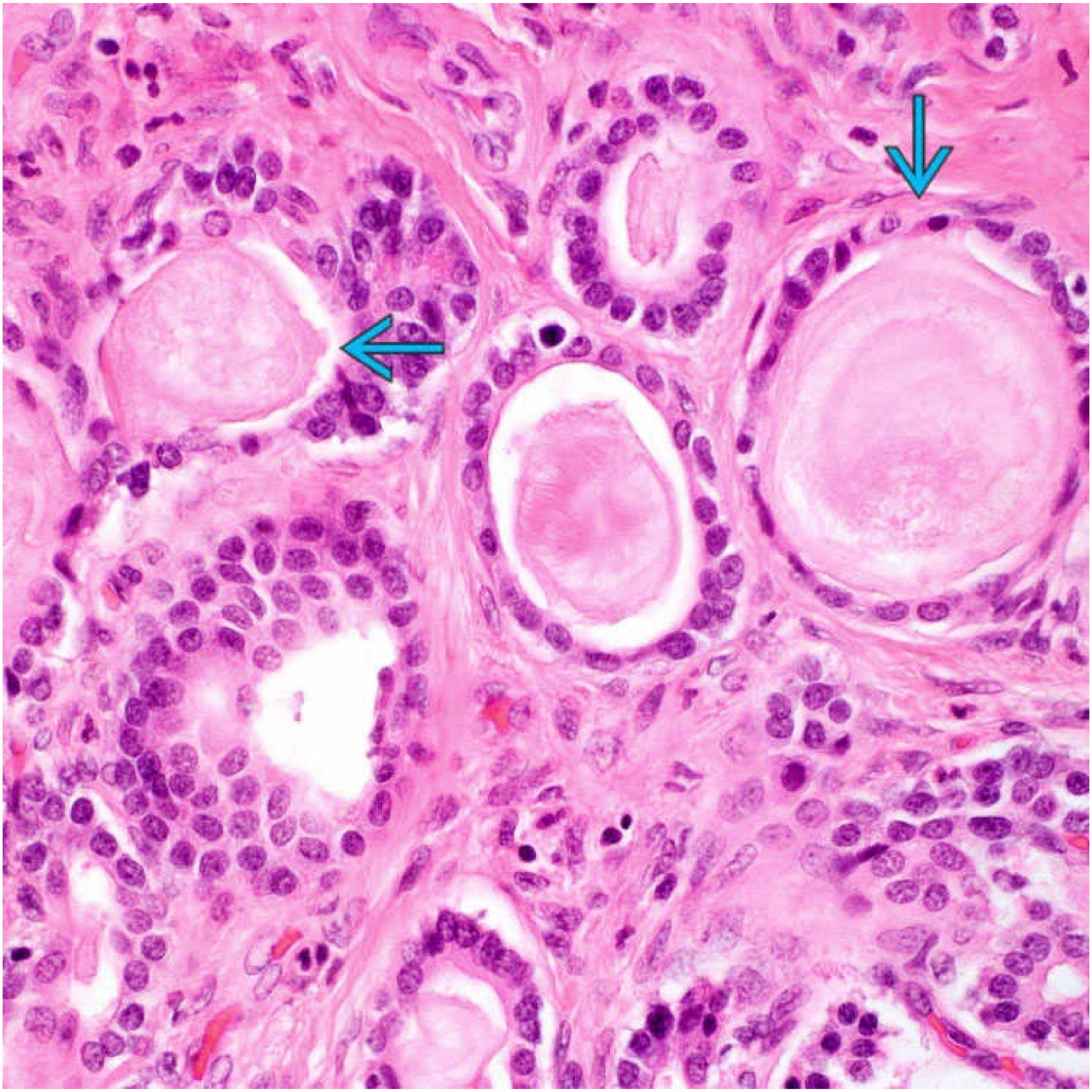
- Accumulation of inspissated eosinophilic secretions in ectatic pancreatic ducts

- Acinar atrophy, cyst formation, fibrosis, and fatty replacement
- Islets of Langerhans are well preserved initially but may decrease in number at later stage of disease

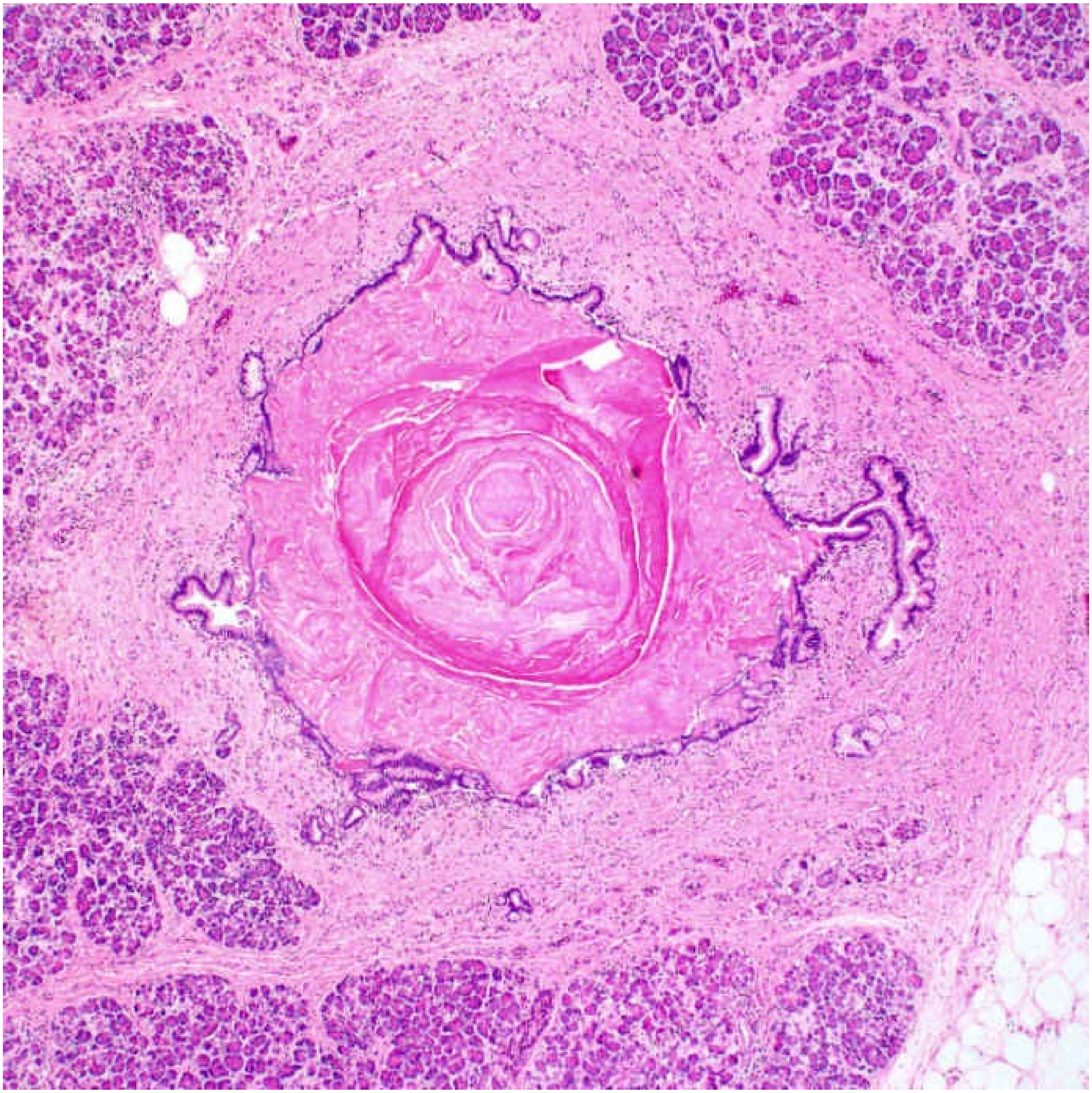


Exocrine Atrophy

This 12-year-old cystic fibrosis (CF) patient underwent liver-pancreas-small bowel transplant for TPN-induced liver failure. The pancreas shows complete atrophy of exocrine glands and mild inflammatory cell infiltrates in fibrous stroma. Eosinophilic concretions are present in small ducts →. Note the presence of islets of Langerhans ↪ .

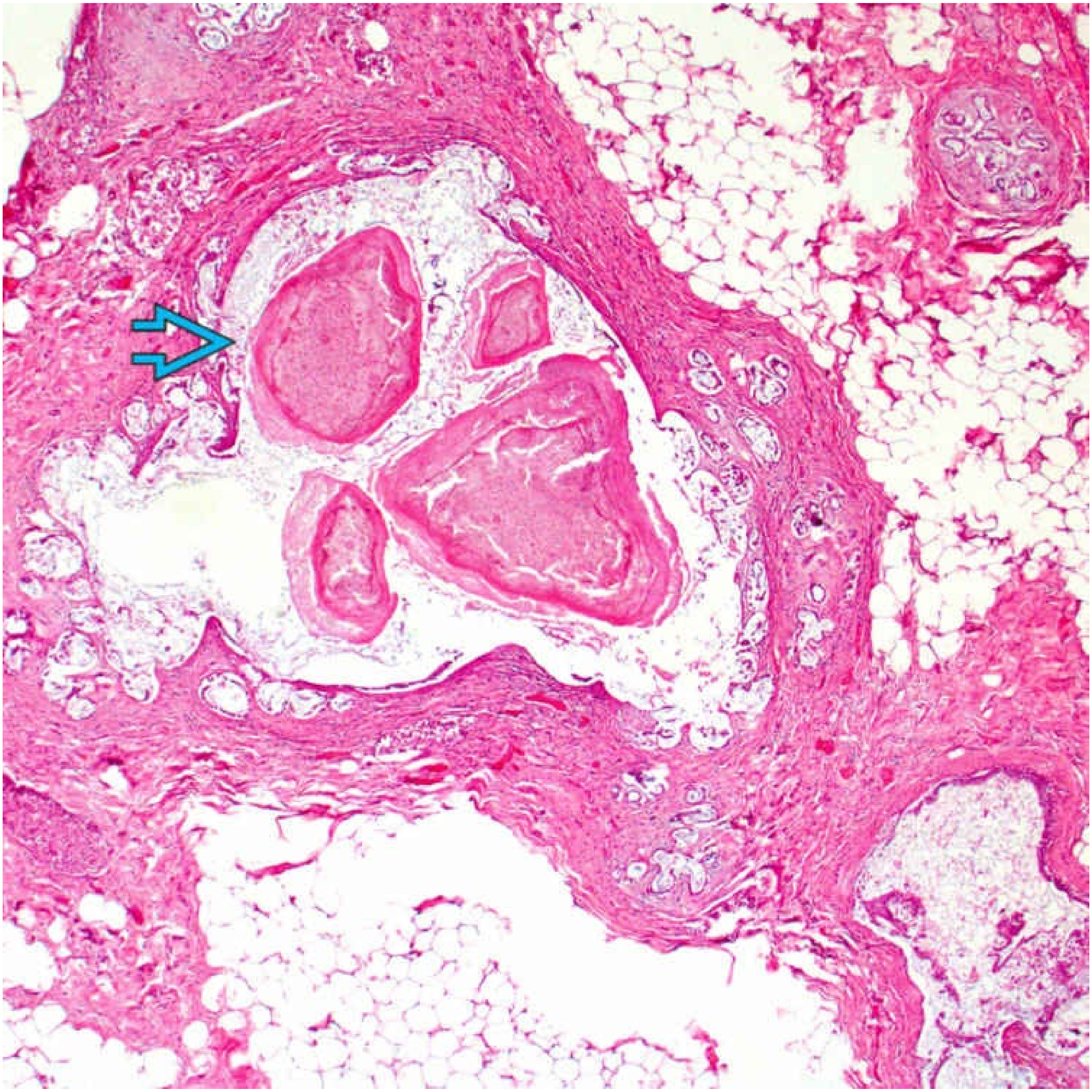


Eosinophilic Concretions
Multiple small ducts are plugged by dense pink eosinophilic secretions, which may have a laminated appearance → .



Dilated Duct With Eosinophilic Secretions

This 1-year-old CF patient underwent multivisceral transplant. Sections of the pancreas show an accumulation of eosinophilic secretions in a dilated duct. The adjacent pancreatic parenchyma in this case does not exhibit significant acinar atrophy or fibrosis.



Fatty Replacement
This advanced case shows extensive fatty replacement of the pancreatic parenchyma. The exocrine glands and islets of Langerhans are completely absent. Note the presence of a cystically dilated duct with eosinophilic concretions .

TERMINOLOGY

Abbreviations

• Cystic fibrosis (CF)

Synonyms

• Mucoviscidosis

Definitions

- Genetic disorder affecting fluid secretion in exocrine glands and epithelial cells lining respiratory, pancreaticobiliary, gastrointestinal, and reproductive tracts
- Disease name refers to pathologic findings of cysts and fibrosis in pancreas

ETIOLOGY/PATHOGENESIS

Mutations of Cystic Fibrosis Transmembrane Conductance Regulator Gene

- Located on chromosome 7q31.2
  - Encodes chloride ion channel protein that regulates fluid balance across epithelial cells
  - > 1,800 mutations have been identified
  - Most common mutation is ΔF508, seen in 70% of CF patients
  - Defective chloride transport leads to thick and tenacious fluid secretions
  - – Blockage of exocrine pancreatic ducts
  - – Damage of pancreatic tissue by accumulated digestive enzymes

CLINICAL ISSUES

Epidemiology

- Incidence
  - Most common autosomal recessive disorder in Caucasians, affecting 1:2,000-3,000 newborns
  - Less common in other ethnic populations
  - Exocrine pancreatic insufficiency occurs in majority (85-90%) of CF patients
- Age
  - Pancreas abnormalities can be seen as early as 32- to 38-weeks gestation and progressively worsen with age

Presentation

- Malabsorption due to exocrine pancreatic insufficiency
  - Steatorrhea
  - Deficiency of fat-soluble vitamins A, D, E, and K
  - Failure to thrive
- Insulin-dependent diabetes mellitus occurs in 25% of CF patients, mostly as adults
- Extrapancreatic presentations
  - Meconium ileus
  - Skin has salty taste
  - Chronic airway infections beginning at early age
  - Infertility

Laboratory Tests

- Sweat chloride test
- Genetic testing
- Newborn screening for early diagnosis

Treatment

- Enzyme replacement
- Vitamin and mineral supplementation
- Antibiotics for infections
- Pancreas or pancreas-liver-lung transplantation
- Potential benefit of gene therapy and targeted therapy with small molecules

Prognosis

- Average life expectancy is 37-48 years in developed countries, and continues to increase
- Lung problems responsible for 80% of deaths

IMAGING

General Features

- Atrophic pancreatic parenchyma, fatty replacement, and cyst formation
- Stricture of intrapancreatic common bile duct
- Cholelithiasis

MACROSCOPIC

General Features

- Small, firm, and nodular pancreas, often with cystic spaces and fatty replacement

MICROSCOPIC

Histologic Features

- Accumulation of inspissated eosinophilic secretions in ectatic pancreatic ducts
    - May be laminated or calcified
- Acinar atrophy, cyst formation, fibrosis, and fatty replacement
    - Flattening of ductal epithelial cells; squamous metaplasia may be seen
    - Complete or near complete cystic transformation leads to pancreatic cystosis
    - Extensive fatty replacement may lead to lipomatous hypertrophy
- Islets of Langerhans are well preserved initially but may decrease in number at later stage of disease
- Inflammatory cells, such as lymphocytes and neutrophils, may be seen in fibrous tissue

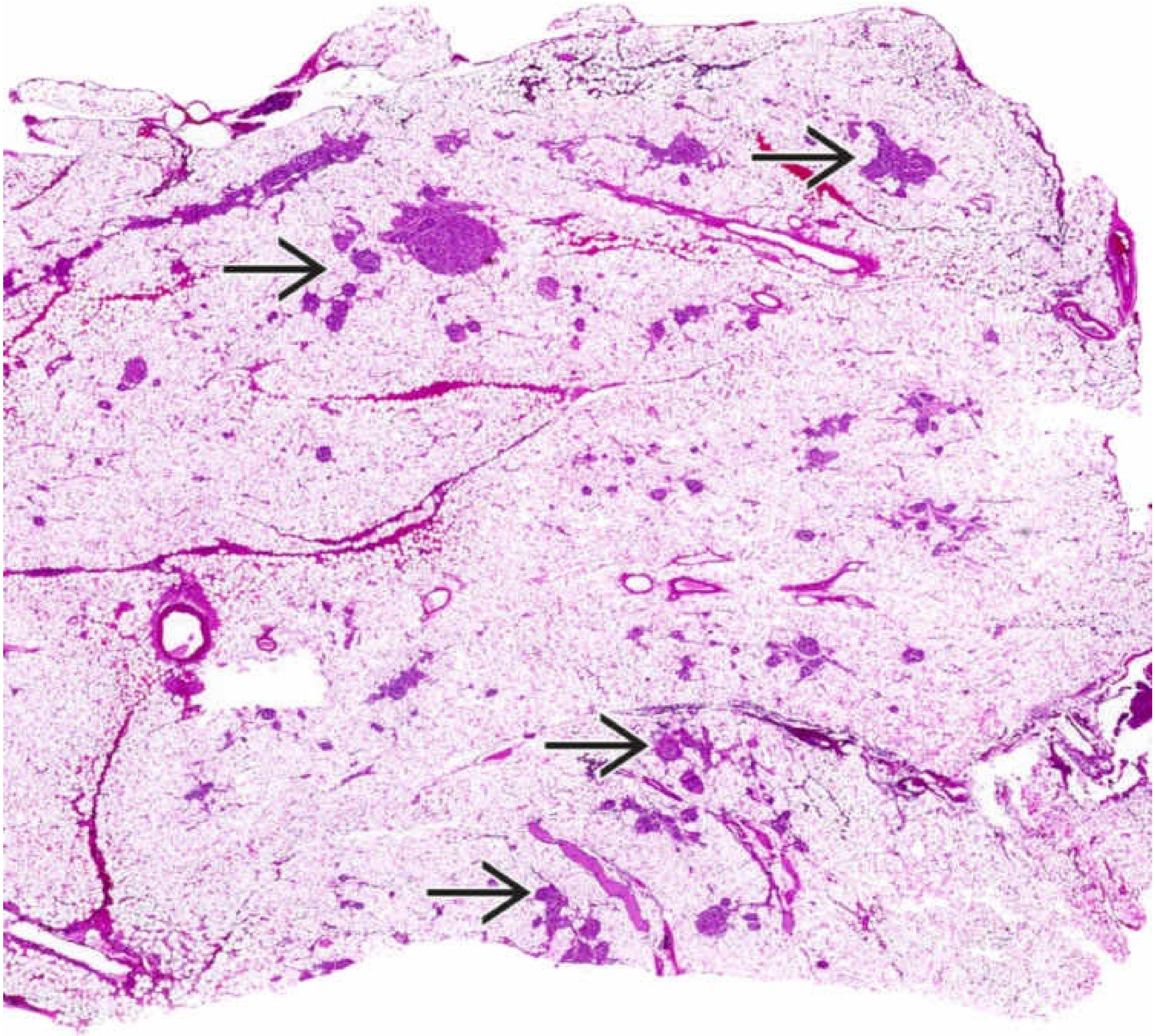
DIFFERENTIAL DIAGNOSIS

Other Forms of Chronic Pancreatitis

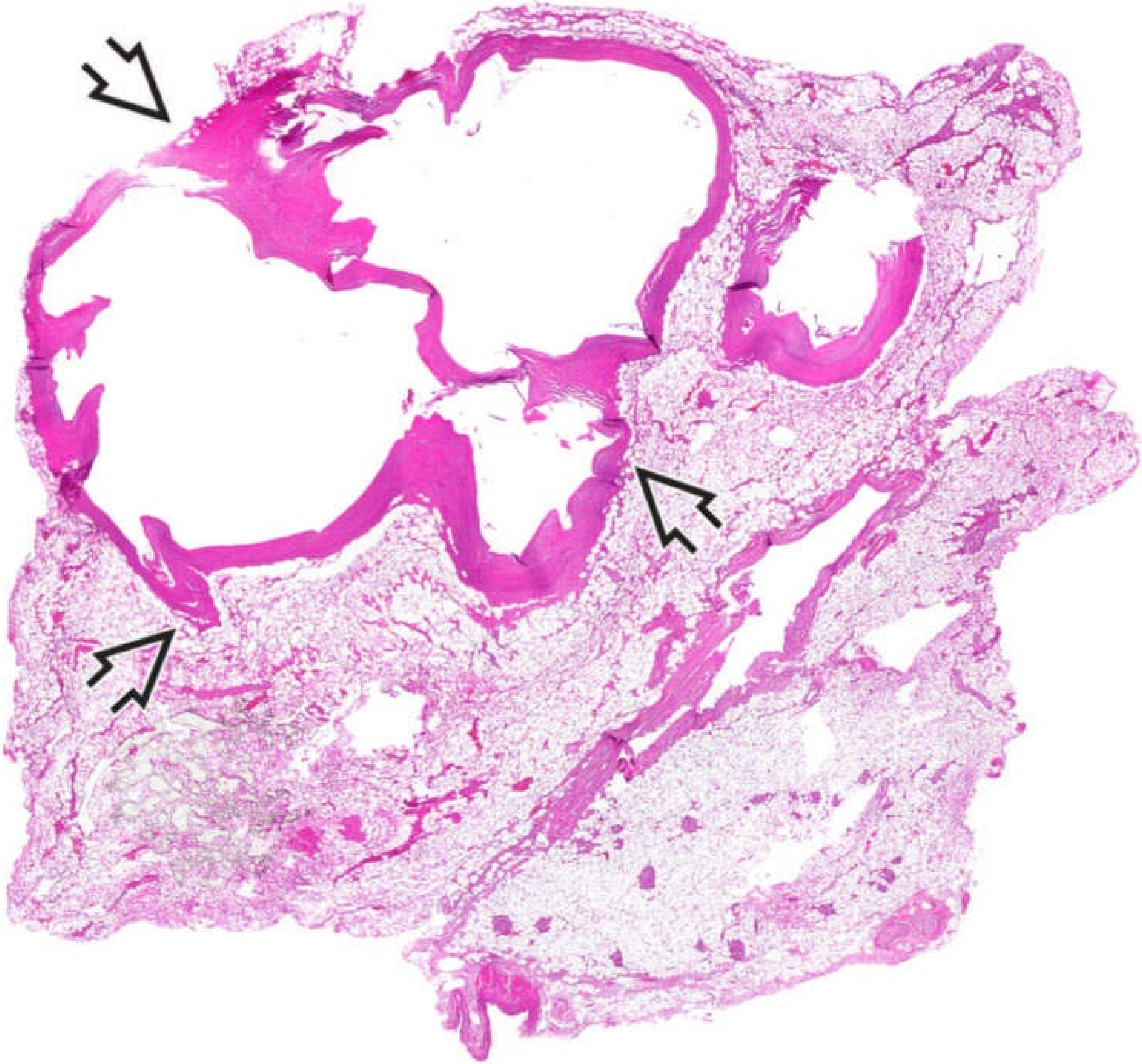
- Older age at onset
- Lack of extrapancreatic signs and symptoms of CF

Cystic Pancreatic Neoplasms

- Older age at onset
- Lack of extrapancreatic signs and symptoms of CF
- Cysts are usually larger and lined by neoplastic cells

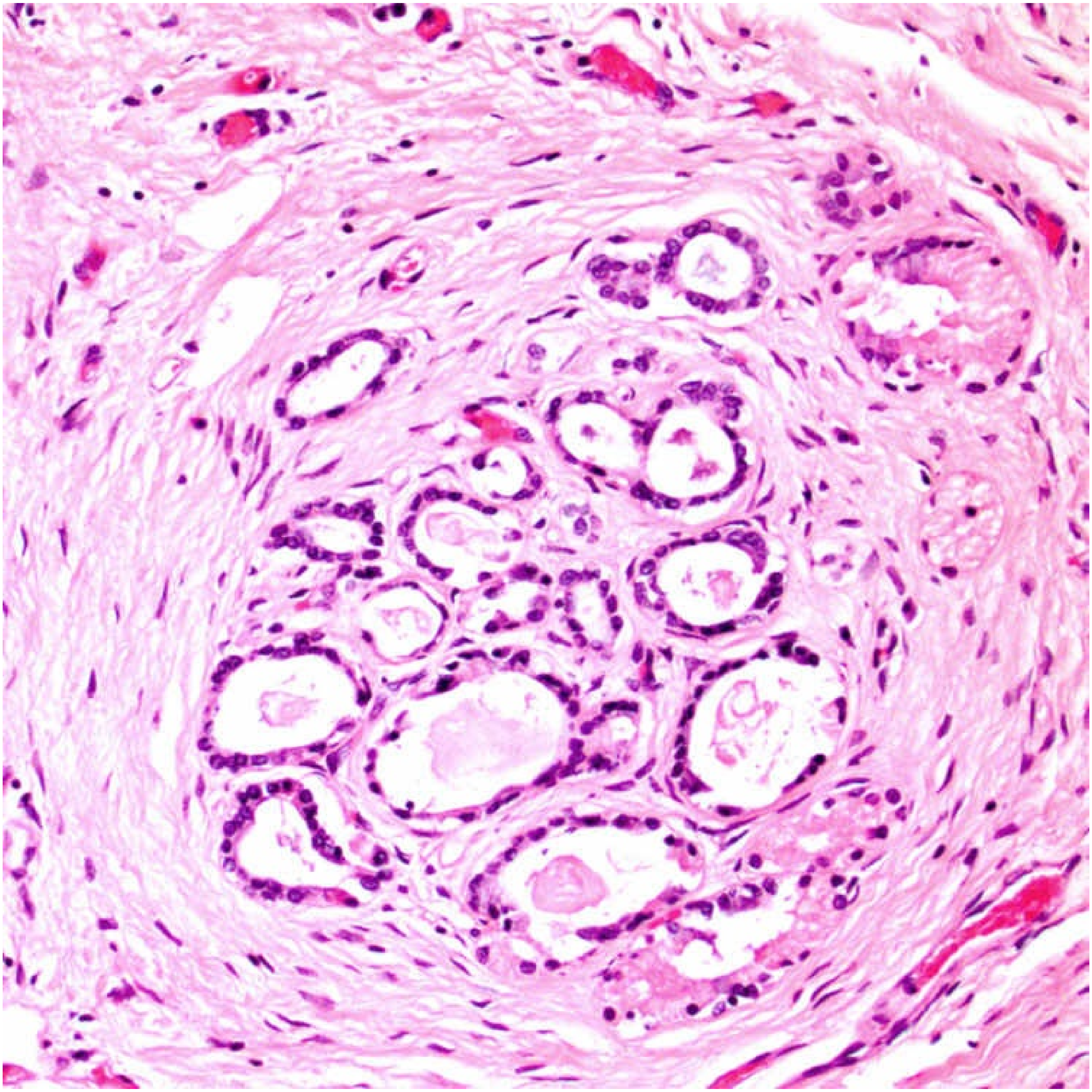


At the advanced stage of disease, total atrophy of the exocrine portion of the pancreas may occur, leaving only islets → within a fibrofatty stroma.



This case shows cyst formation ➪ in a background of fatty replacement of the pancreatic parenchyma.

This pancreas from a 32-year-old CF patient demonstrates complete replacement of the parenchyma by fat. Note that the overall lobular macroscopic architecture of the pancreas is well-maintained.


Dilatation of ducts, many of which contain eosinophilic concrete mucous secretions, is common in CF.

SELECTED REFERENCES

1.Deignan, JL, et al. Molecular diagnosis of cystic fibrosis. *Curr Protoc Hum Genet*. 2016; 88:9.28.1–9.28.6.

2.Gibson-Corley, KN, et al. Pancreatic pathophysiology in cystic fibrosis. *J Pathol*. 2016; 238(2):311–320.

3.Augarten, A, et al. The changing face of the exocrine pancreas in cystic fibrosis: the correlation

between pancreatic status, pancreatitis and cystic fibrosis genotype. *Eur J Gastroenterol Hepatol*. 2008; 20(3):164–168.

Nesidioblastosis

KEY FACTS

Terminology

- Pathologic changes in pancreatic islets associated with functional dysregulation of β cells that leads to hyperinsulinemic hypoglycemia

Etiology/Pathogenesis

- Neonates
  - Mutations of *ABCC8* or *KCNJ11* genes encoding subunits of ATP-sensitive potassium channel in majority of cases
  - Mutations of *GCK*, *GLUD1*, *HSD17B10* (SCHAD), *SLC16A1*, *HNF1A*, *HNF4A*, *or UCP2* genes in minority of cases
- Adults
  - Metabolic and hormonal changes due to substantial weight loss after gastric bypass surgery
  - Idiopathic

Clinical Issues

- Symptoms and signs of hypoglycemia

Microscopic

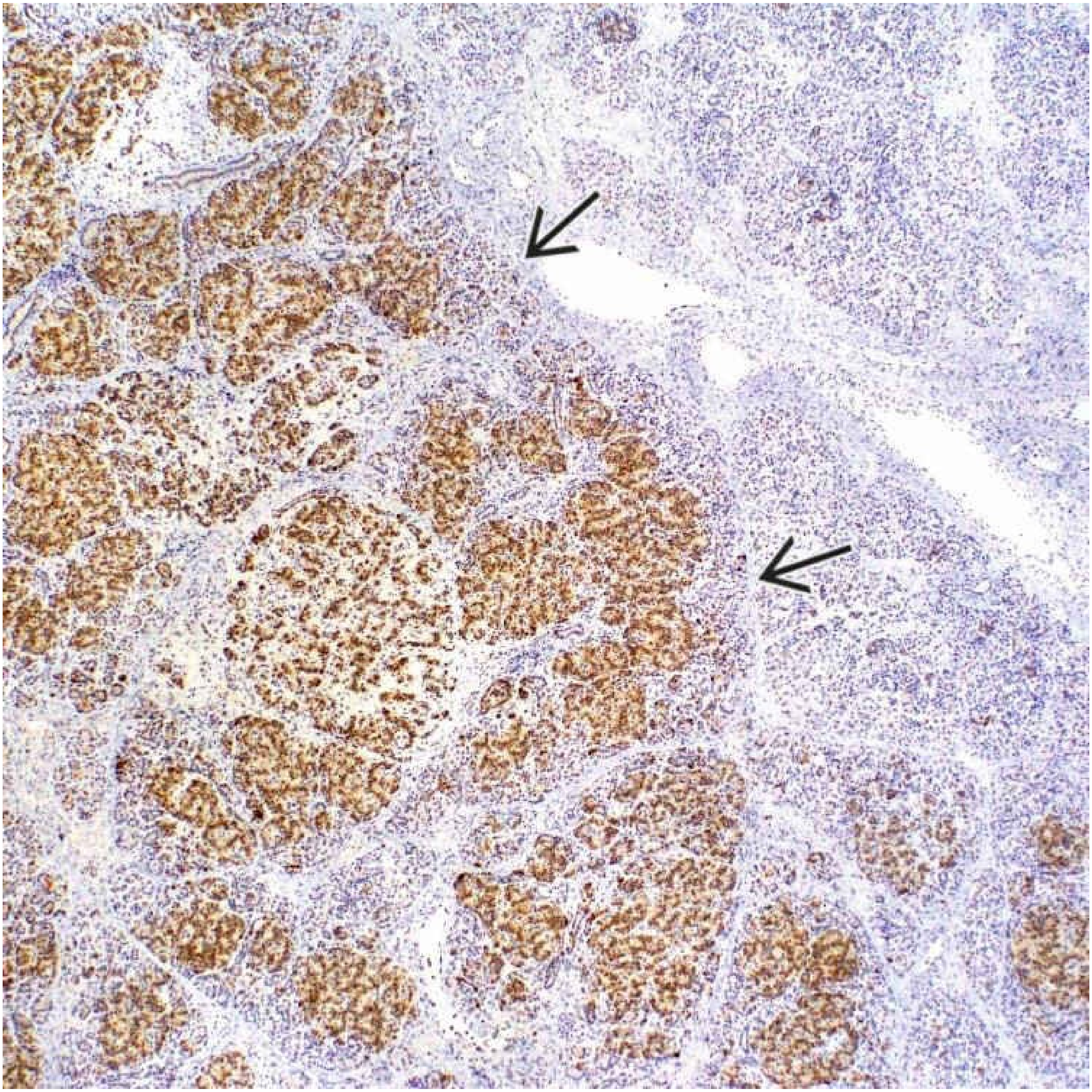
- Neonatal focal nesidioblastosis (NB)
  - Nodular lesion consisting of confluent clusters of endocrine cells (adenomatous hyperplasia)
  - Presence of enlarged, hyperchromatic islet cell nuclei within lesion
  - Normal islets with no nuclear enlargement outside lesion
- Neonatal diffuse NB
  - Enlarged, hyperchromatic islet cell nuclei throughout entire pancreas
- Adult NB
  - Similar to neonatal diffuse NB

Ancillary Tests

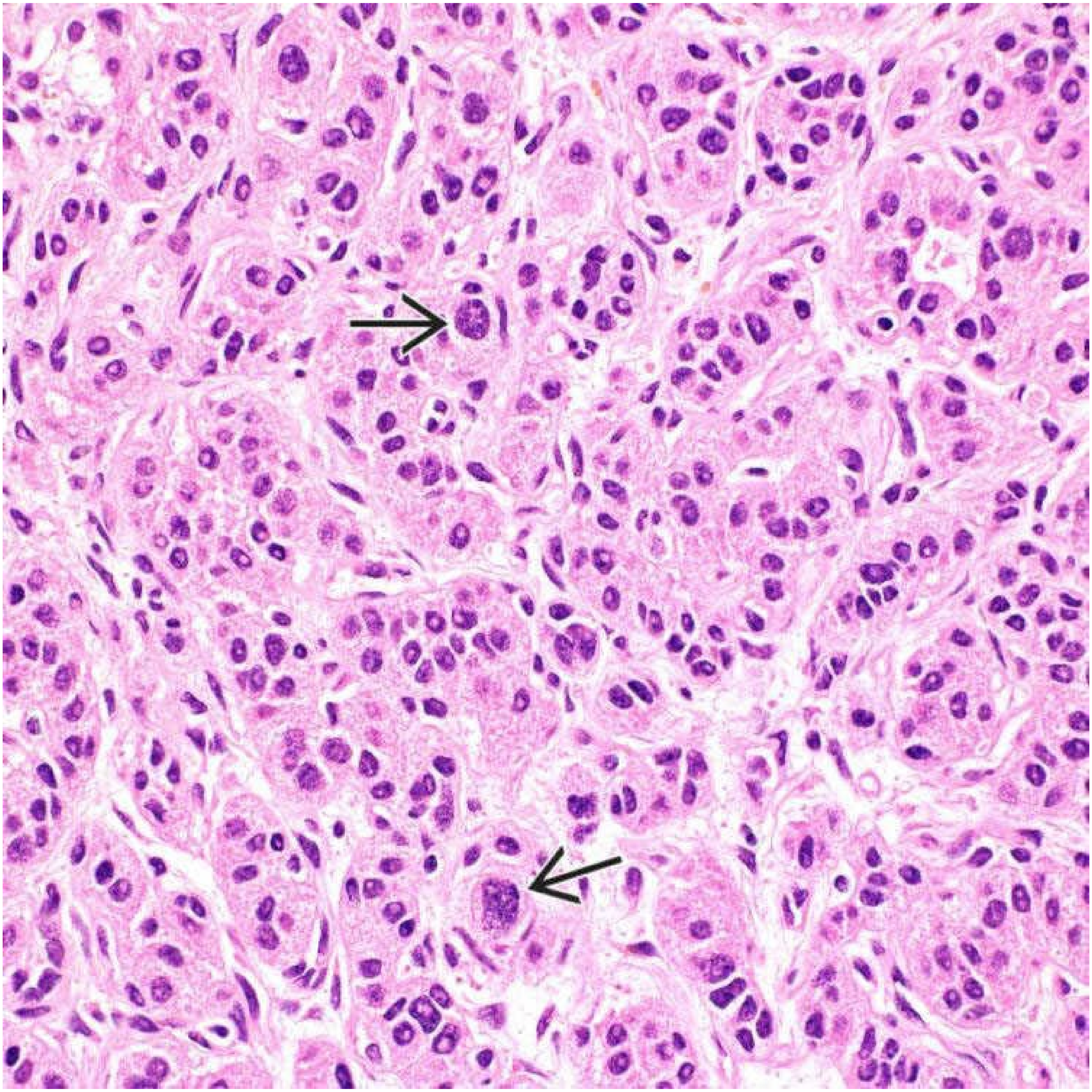
- Sequencing of NB-related genes helps diagnosis, classification, and treatment decision

Top Differential Diagnoses

- Insulinoma

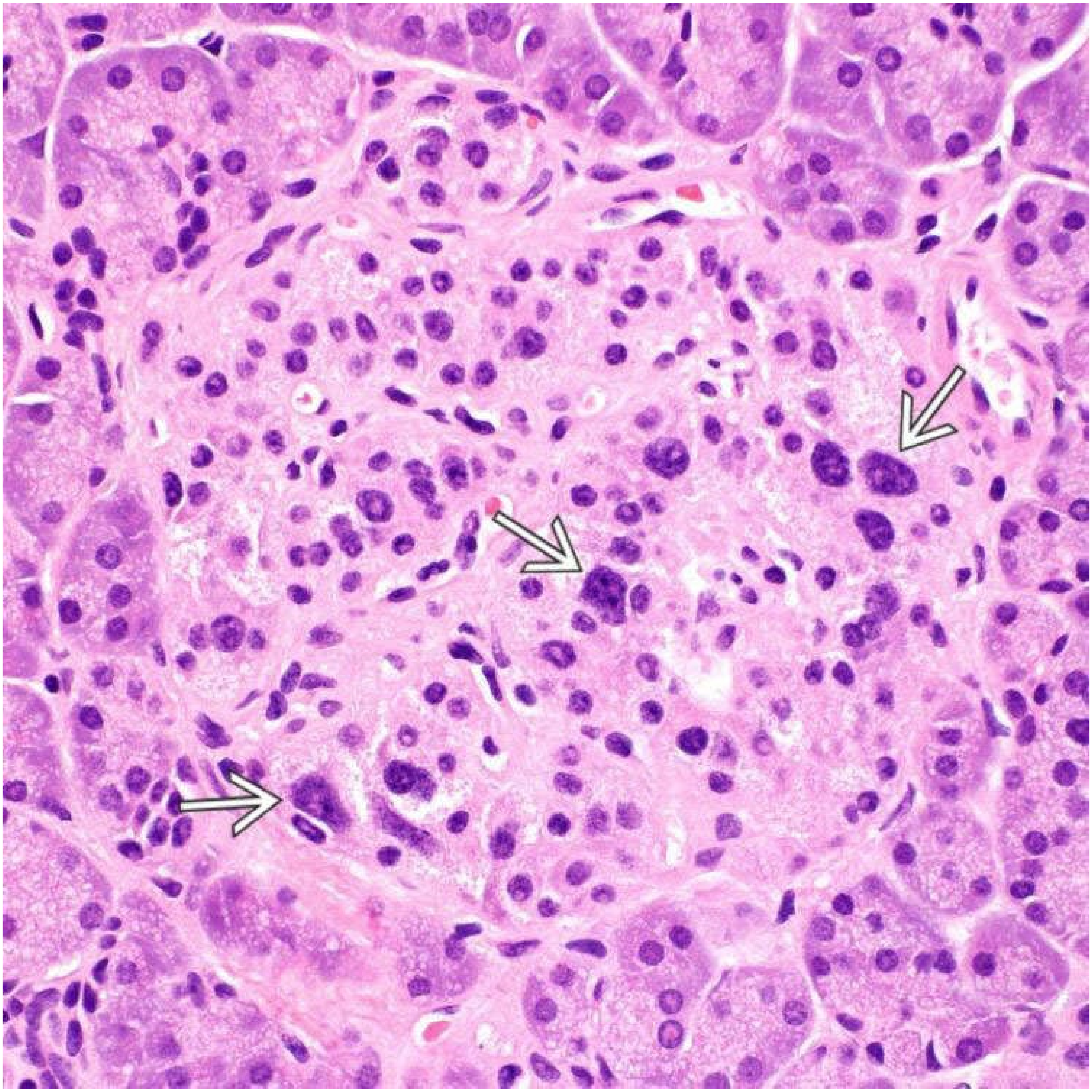


Focal Nesidioblastosis
This 0.8-cm nodule detected by image studies in the distal pancreas was from a 5-week-old girl who presented with persistent hypoglycemia. Preoperative genetic testing was consistent with focal nesidioblastosis (NB). The nodule is well demarcated and consists of clusters of endocrine cells, as highlighted by chromogranin stain →.



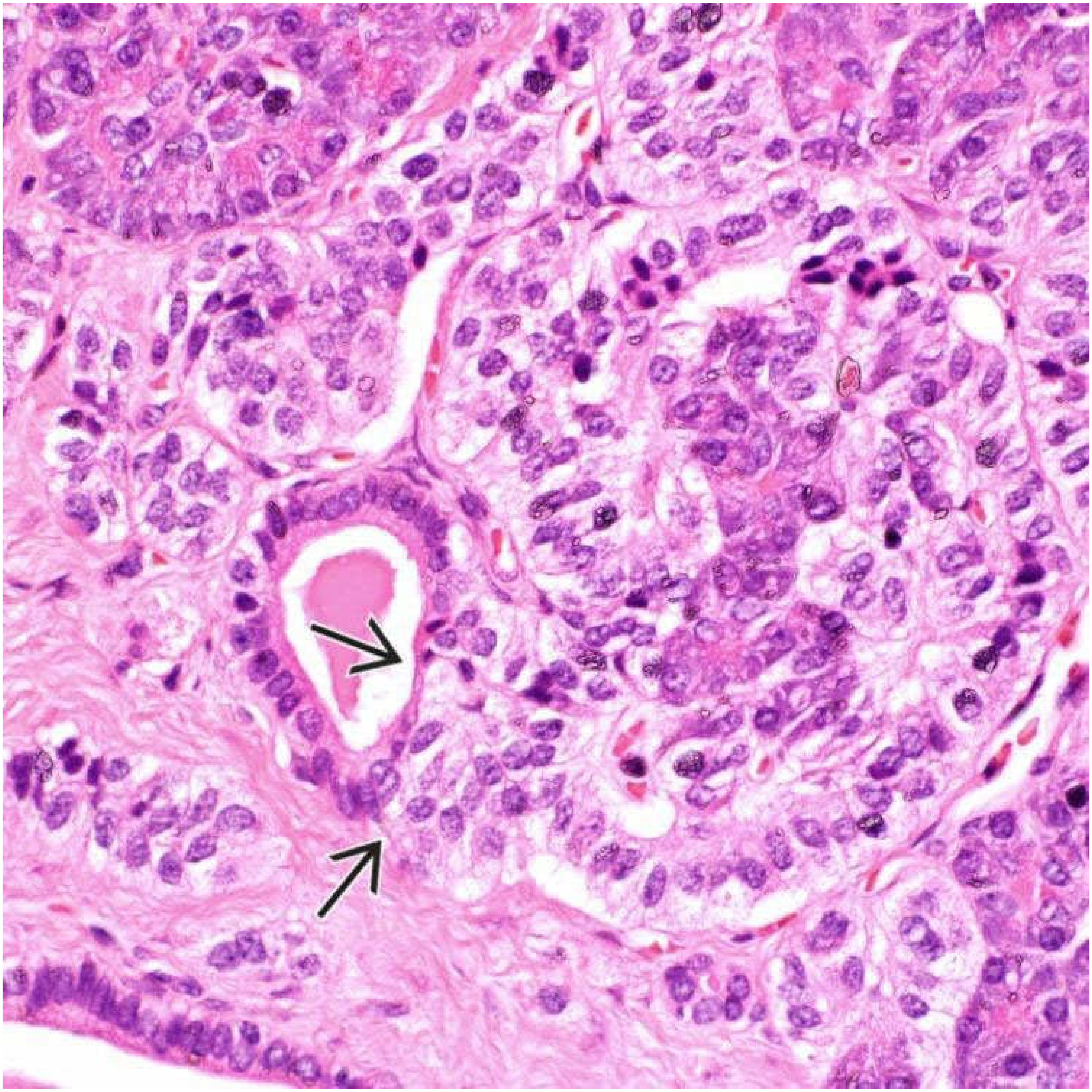
Enlarged Islet Cells

This frozen section was performed on a pancreatic nodule excised from a neonate with hyperinsulinism. It shows a few endocrine cells with enlarged nuclei →, consistent with focal NB.



Diffuse Nesidioblastosis

This total pancreatectomy from a neonate with diffuse NB shows multiple islet cells with enlarged and hyperchromatic nuclei ⇒, which are 3x larger than normal. The size and shape of islets do not appear abnormal in this case, but the number is increased.



Ductuloinsular Complex
This microphotograph shows close association of islet cells with ducts and budding off of cells from a duct to form new islets →. This phenomenon was originally termed nesidioblastosis, which now has a different pathologic meaning.

TERMINOLOGY

Abbreviations

• Nesidioblastosis (NB)

Synonyms

• Hyperinsulinemic hypoglycemia

- Congenital hyperinsulinism

Definitions

- Pathologic changes in pancreatic islets associated with functional dysregulation of β cells that leads to hyperinsulinemic hypoglycemia

ETIOLOGY/PATHOGENESIS

Neonate Nesidioblastosis

- Mutations of *ABCC8* or *KCNJ11* genes encoding subunits of ATP-sensitive potassium channel
  - Diffuse NB
    - Homozygous recessive or compound heterozygous *ABCC8 or KCNJ11* mutations
  - Focal NB
    - Heterozygous paternally inherited *ABCC8 or KCNJ11* mutations and somatic loss of maternal 11p15
    - Rarely, paternal allele duplication of chromosome 11
- Other uncommon genetic causes
  - Mutations of *GCK*, *GLUD1*, *HSD17B10* (SCHAD), *SLC16A1*, *HNF1A*, *HNF4A*, *or UCP2* genes

Adult Nesidioblastosis

- Metabolic and hormonal changes due to substantial weight loss after gastric bypass surgery
- Idiopathic

CLINICAL ISSUES

Epidemiology

- Incidence
  - Neonate NB
    - Familial: 1 in 2,500 births
    - Sporadic: 1 in 50,000 births
  - Adult NB
    - Unknown but thought to be low

Presentation

- Symptoms and signs of hypoglycemia
  - Usually postprandial for adult NB

Laboratory Tests

- High serum insulin &/or C-peptide levels in presence of hypoglycemia

Treatment

- Surgical approaches
  - Focal neonatal NB
  - – Limited resection or partial pancreatectomy
- Diffuse neonatal and adult NB
- – Total or near-total pancreatectomy
- Drugs
  - Diazoxide and octreotide
    - – Effective for *GCK* or *GLUD1* -mutated neonatal NB
  - Sirolimus (mTOR inhibitor)

Prognosis

- Resection is curative for neonatal focal NB
- Insulin-dependent diabetes following total pancreatectomy

MACROSCOPIC

General Features

- Neonatal focal NB may produce detectable nodule (typically < 1 cm)

MICROSCOPIC

Histologic Features

- Neonatal focal NB
  - Nodular lesion consisting of confluent clusters of endocrine cells (adenomatous hyperplasia)
  - – All types of endocrine cells are represented, but percentage of β cells is higher than normal (70-90% vs. 50%)
  - – Presence of enlarged, hyperchromatic islet cell nuclei
  - – Presence of intermixed exocrine cells
- Normal islets with no nuclear enlargement outside lesion
- Rarely multifocal
- Neonatal diffuse NB
  - Enlarged, hyperchromatic islet cell nuclei throughout entire pancreas
- Adult NB
  - Similar to neonatal diffuse NB
- Other described islet abnormalities

    - Increased islet number
    - Enlarged islet size (> 300 μm)
    - Irregular islet contour
    - Ductuloinsular complex (close association with duct)
- Frozen sections to guide extent of resection
    - Multiple random pancreatic samples need to be examined if focal lesion is not identified
    - Presence of enlarged islet cell nuclei indicates diffuse NB; absence suggests focal NB

ANCILLARY TESTS

Immunohistochemistry

- Chromogranin highlights confluent islets in focal NB

Genetic Testing

- Sequencing of NB-related genes helps diagnosis, classification, and treatment decision

DIFFERENTIAL DIAGNOSIS

Insulinoma

- Well-demarcated lesion composed solely of endocrine cells
- Does not express other hormones but insulin
- Usually presents with fasting hypoglycemia

Normal Pancreas

- Islets in neonates (particularly those of diabetic mothers) are more prominent than those in later life

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Frozen sections to guide extent of resection
    - Multiple random pancreatic samples need to be examined if focal lesion cannot be identified
    - Presence of enlarged islet cell nuclei indicates diffuse form
    - Absence of enlarged islet cell nuclei suggests focal form

SELECTED REFERENCES

1. Roženková, K, et al. The diagnosis and management of hyperinsulinaemic hypoglycaemia. *J Clin Res Pediatr Endocrinol*. 2015; 7(2):86–97.
2. Dravecka, I, et al. Nesidioblastosis in adults. *Neoplasma*. 2014; 61(3):252–256.

Choledochal Cyst

KEY FACTS

Terminology

- Cystic dilatation of biliary tract, usually extrahepatic

Etiology/Pathogenesis

- Majority of patients have abnormal pancreaticobiliary junction
  - Possibly congenital malformation

Clinical Issues

- Usually presents in childhood before age 10
  - 75% of patients are female
  - Very common in Asian populations, particularly in Japan
- Jaundice, abdominal pain, mass are common findings
- Presentation
  - Classic presentation (minority of patients) is RUQ mass, intermittent abdominal pain, jaundice
  - Infants usually present with jaundice
    - – Infants at particular risk for chronic low-grade biliary obstruction leading to cirrhosis
- Increased risk of carcinoma (usually adenocarcinoma)

Imaging

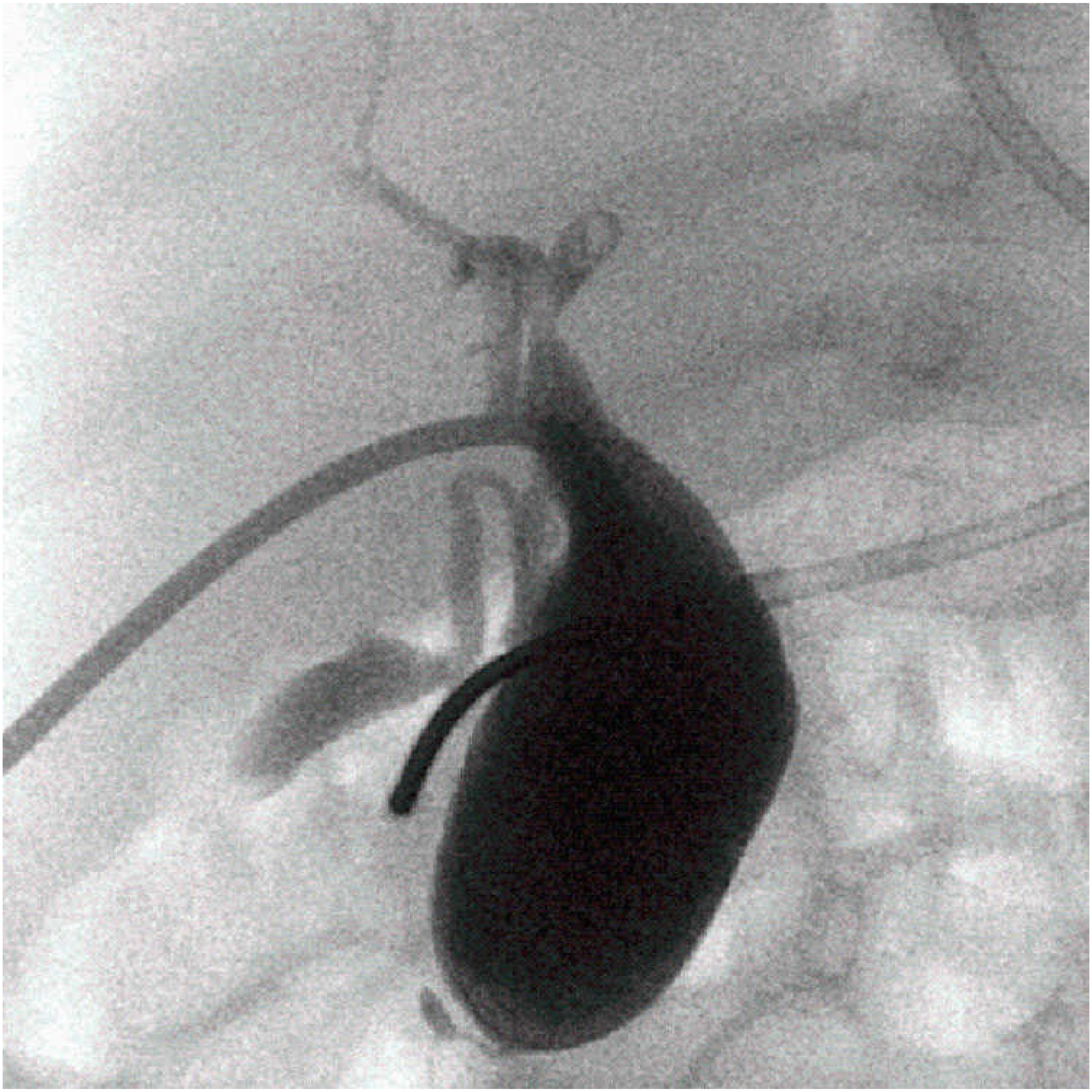
- Cholangiography is definitive diagnostic procedure

Macroscopic

- Todani classification
  - Type I (segmental or diffuse fusiform dilatation of common bile duct) is most common
- Range from few cm to > 15 cm

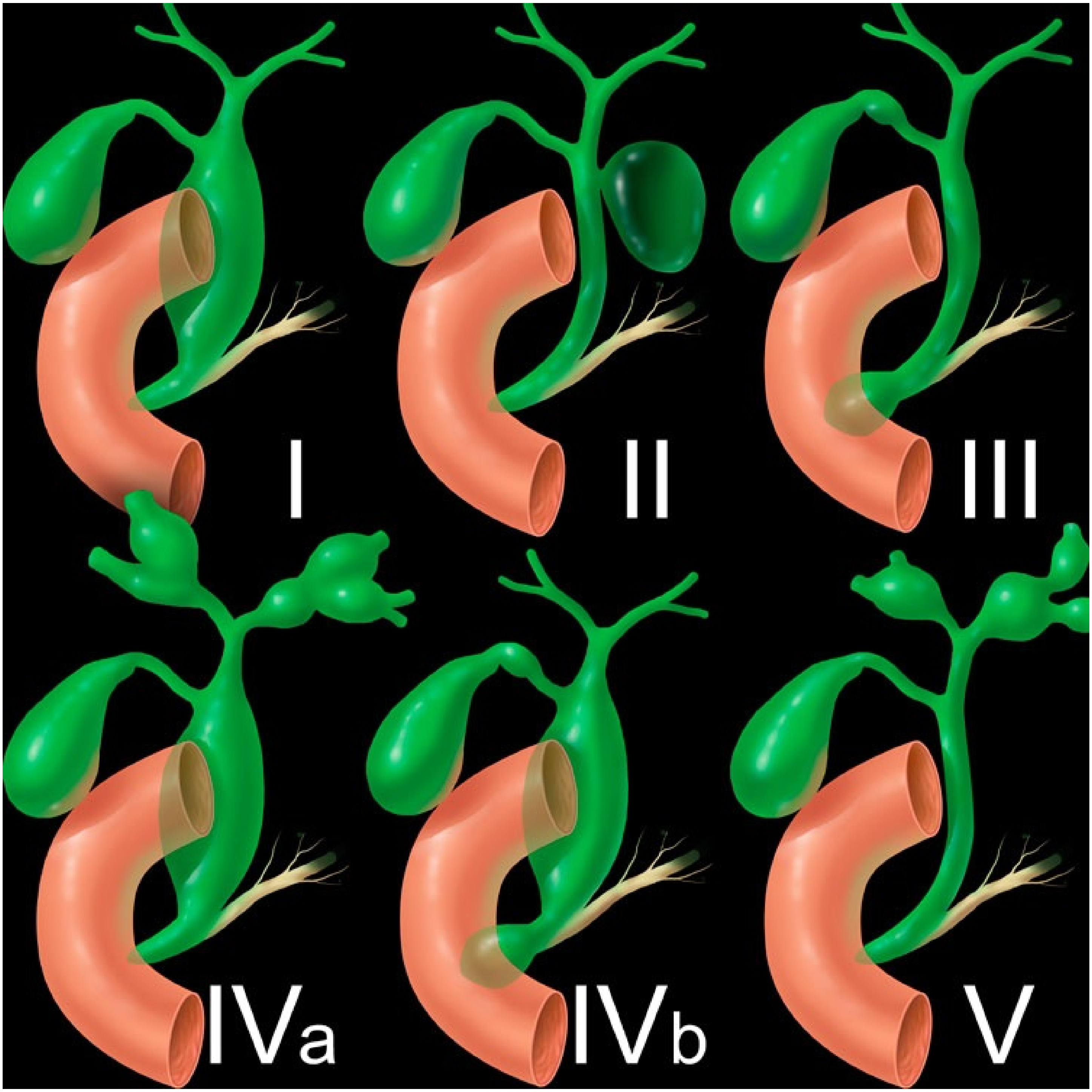
Microscopic

- Thickened, fibrotic cyst wall
  - Epithelial lining may be intact or damaged, attenuated, or absent altogether
  - Inflammation often present
- Liver biopsy specimen shows nonspecific changes of acute or chronic biliary obstruction

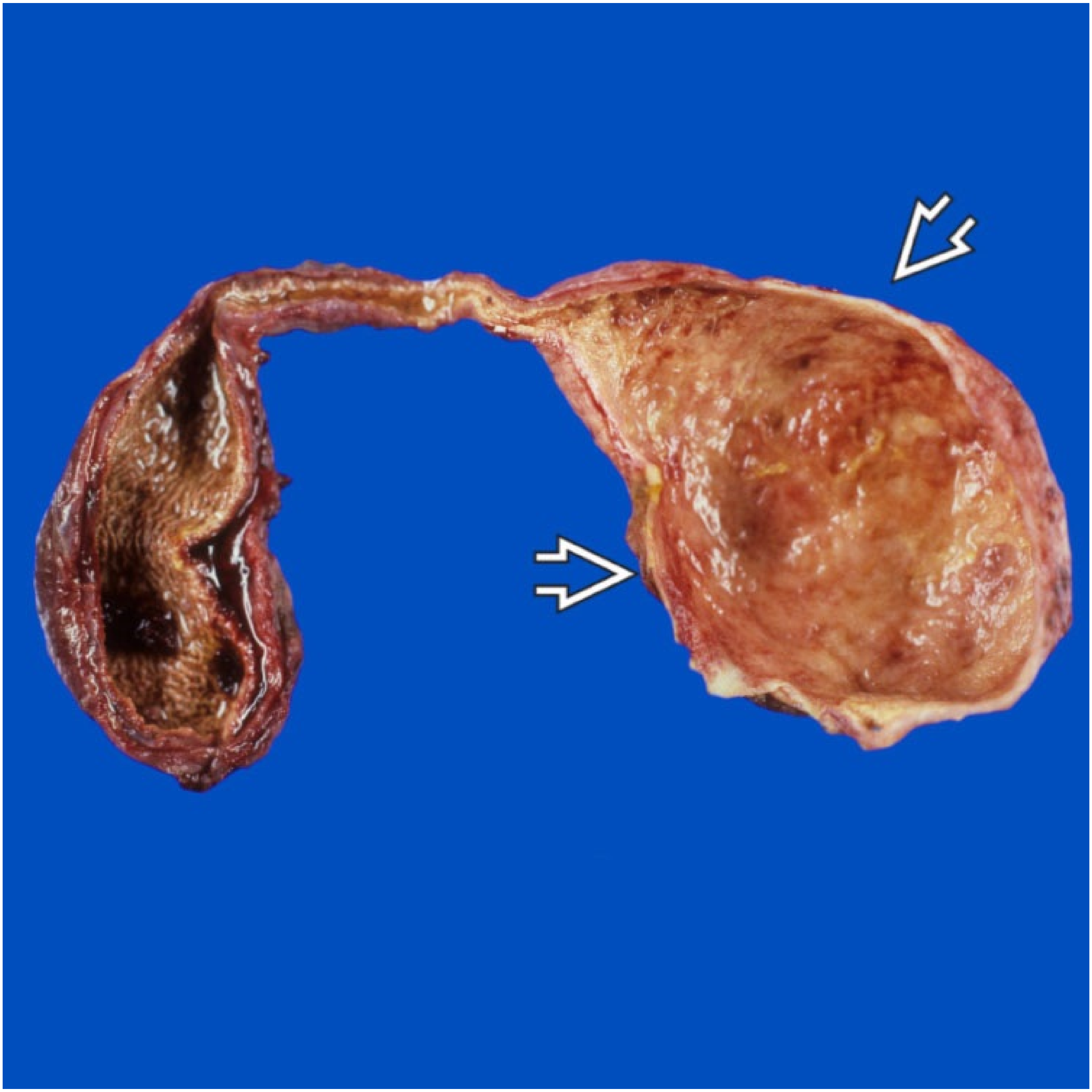


Cholangiogram

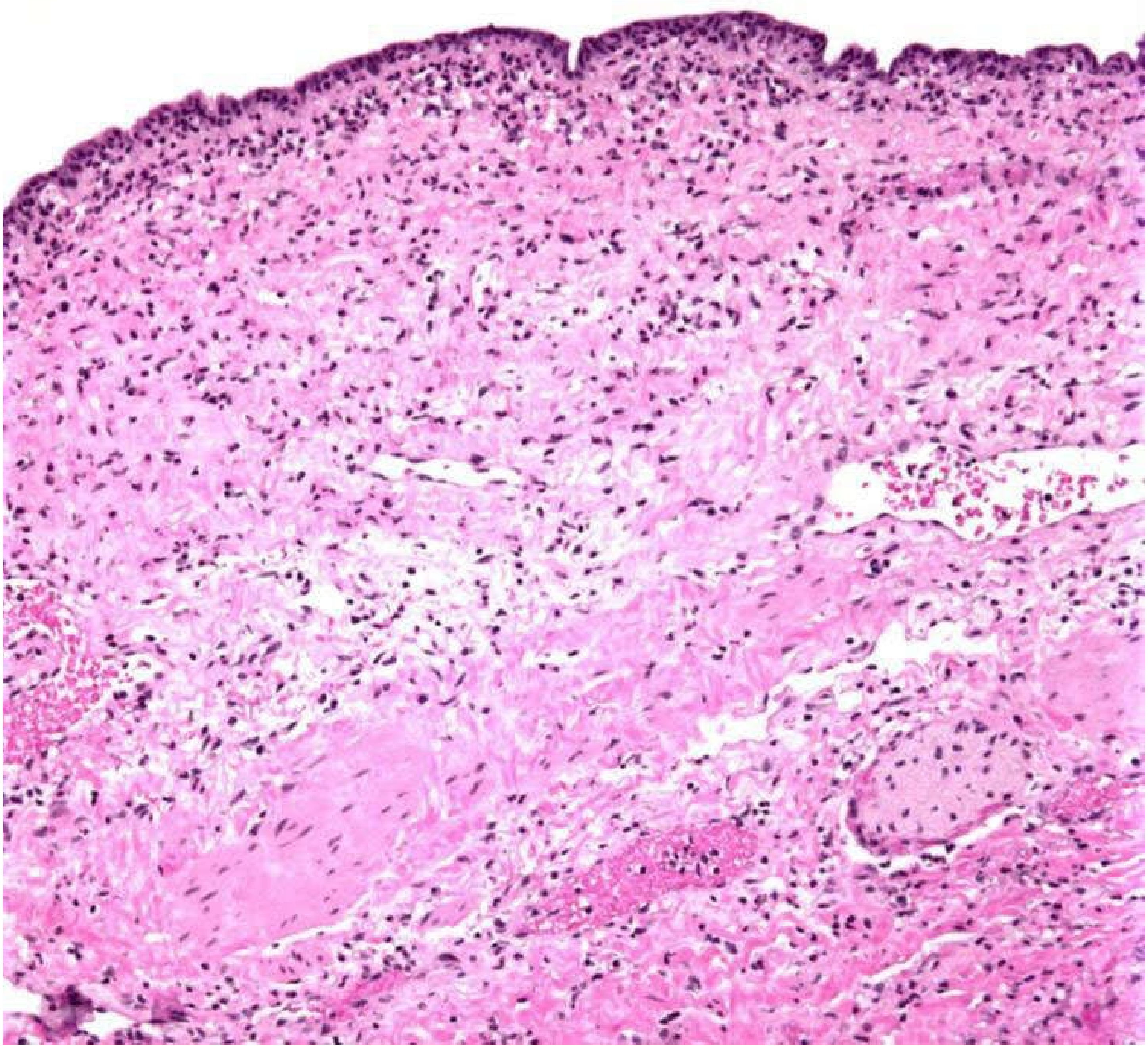
Anteroposterior radiograph during percutaneous cholangiogram shows a fusiform dilatation of the common bile duct with rapid change in caliber at the sphincter of Oddi, confirming type I choledochal cyst.



Todani Classification
The Todani classification includes types I (dilated common duct), II (diverticulum), III (choledochocele), IVa (extrahepatic cysts and cystic dilatation of intrahepatic ducts), IVb (multiple extrahepatic cysts), and V (multiple intrahepatic cysts).



Gross Resection Specimen
This resection shows a large saccular choledochal cyst on the right of the photograph.



Cyst Wall
This section of a choledochal cyst wall has intact epithelium with underlying mural fibrosis and acute and chronic inflammation.

TERMINOLOGY

Definitions

• Cystic dilatation of biliary tract, usually extrahepatic

ETIOLOGY/PATHOGENESIS

Unknown

- Possible congenital malformation
  - Majority of patients have abnormal pancreaticobiliary junction
    - Long common channel between distal common bile duct and pancreatic duct
    - May allow pancreatic secretions to reflux into bile ducts, possibly causing damage and eventual dilatation
- No specific inheritance pattern
- Occasionally coexists with congenital hepatic fibrosis, biliary dysgenesis, extrahepatic cystic disease

CLINICAL ISSUES

Epidemiology

- Age
  - Usually presents before age 10; can present at any age, however
- Sex
  - 75% of patients are female
- Ethnicity
  - Rare in United States (1 in 13,000 live births)
  - Very common in Asian populations, particularly in Japan

Presentation

- Classic presentation is right upper quadrant mass with intermittent abdominal pain, jaundice
  - Seen in only minority of cases
- Infants usually present with jaundice
  - Acholic stools, hepatomegaly may be present
- Some cases are asymptomatic

Treatment

- Complete excision

Prognosis

- Variable clinical course depending on complications
  - Infants at particular risk for chronic low-grade biliary obstruction leading to cirrhosis
  - Other complications
    - Bile duct perforation
    - Choledocholithiasis
    - Bacterial cholangitis
- Increased risk of carcinoma (usually adenocarcinoma)
  - Up to 20x increased risk over general population
    - ~ 30% of patients with biliary cysts develop carcinoma
  - Risk increases with age

- Cyst itself is most common site for carcinoma to develop (usually posterior wall), but other portions of biliary tree may also be at increased risk

IMAGING

General Features

- Cholangiography is definitive diagnostic procedure

MACROSCOPIC

General Features

- Thickened, fibrotic cyst wall with variably present stones or calcification

Size

- Range from few centimeters to > 15 cm
- Contain from 30-5,000 mL of bile

Anatomic (Todani) Classification

- Type I: Segmental or diffuse fusiform dilatation of common bile duct
  - Most common (75-95% of cases)
- Type II: Supraduodenal diverticulum of common bile duct, usually lateral wall; rest of biliary tree normal
- Type III: Choledochocele that usually occurs within duodenal wall
- Type IV: Multiple extrahepatic bile duct cysts
  - IVa: Associated with Caroli disease-like cystic dilatation of intrahepatic bile ducts
  - IVb: Cysts exclusively extrahepatic
- Type V: Intrahepatic cystic dilatation equivalent to Caroli disease

MICROSCOPIC

Histologic Features

- Thickened, fibrotic cyst wall
  - Chronic inflammation often present
  - Elastic and smooth muscle fibers variably present
- Biliary epithelial lining may be intact or damaged, attenuated, or absent altogether
  - Intestinal metaplasia well described
  - Dysplasia can occur
  - Type III cyst (choledochocele) often lined by duodenal epithelium
- Liver biopsy may show changes of acute or chronic biliary obstruction, including biliary cirrhosis

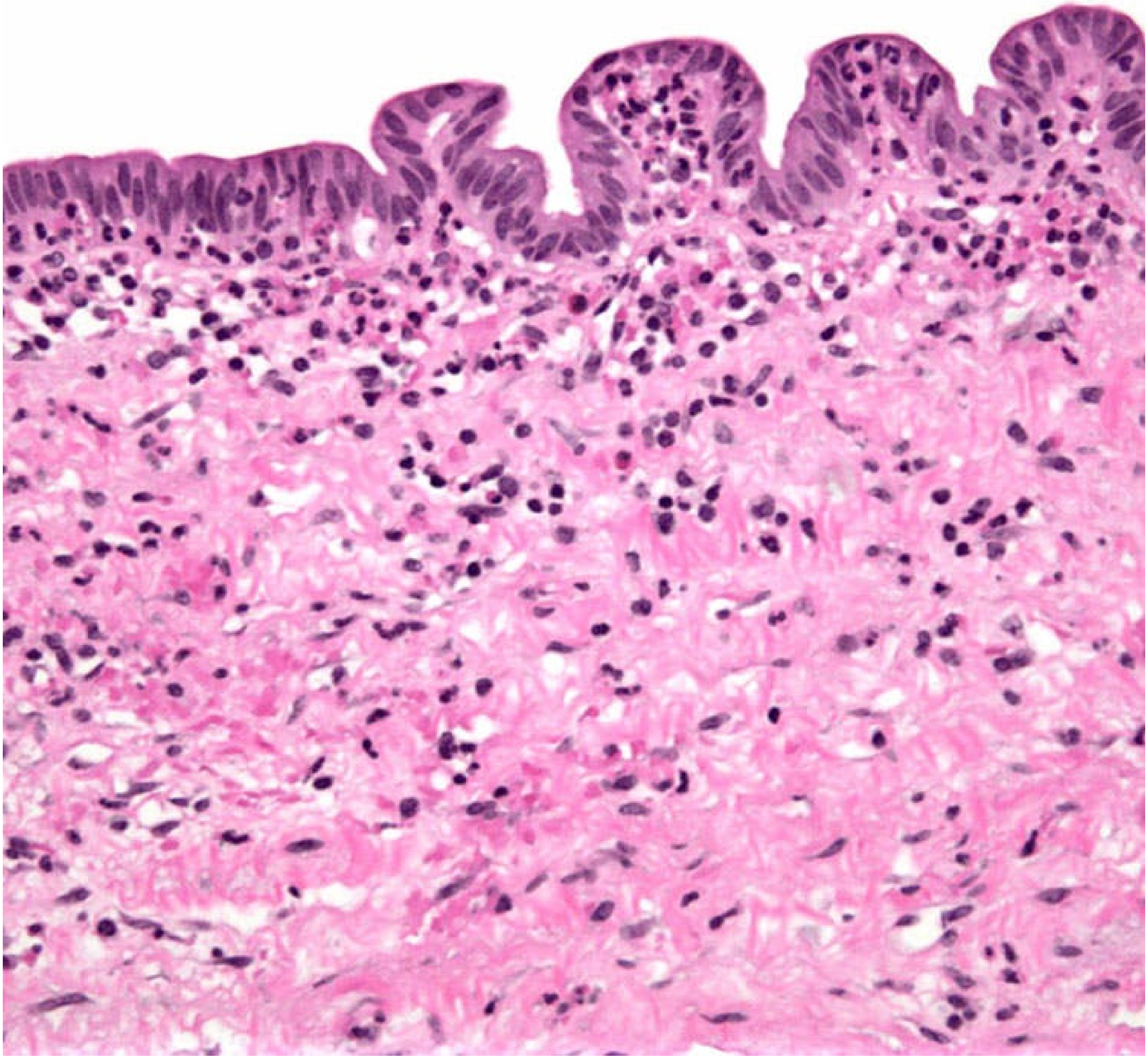
DIFFERENTIAL DIAGNOSIS

Biliary Atresia

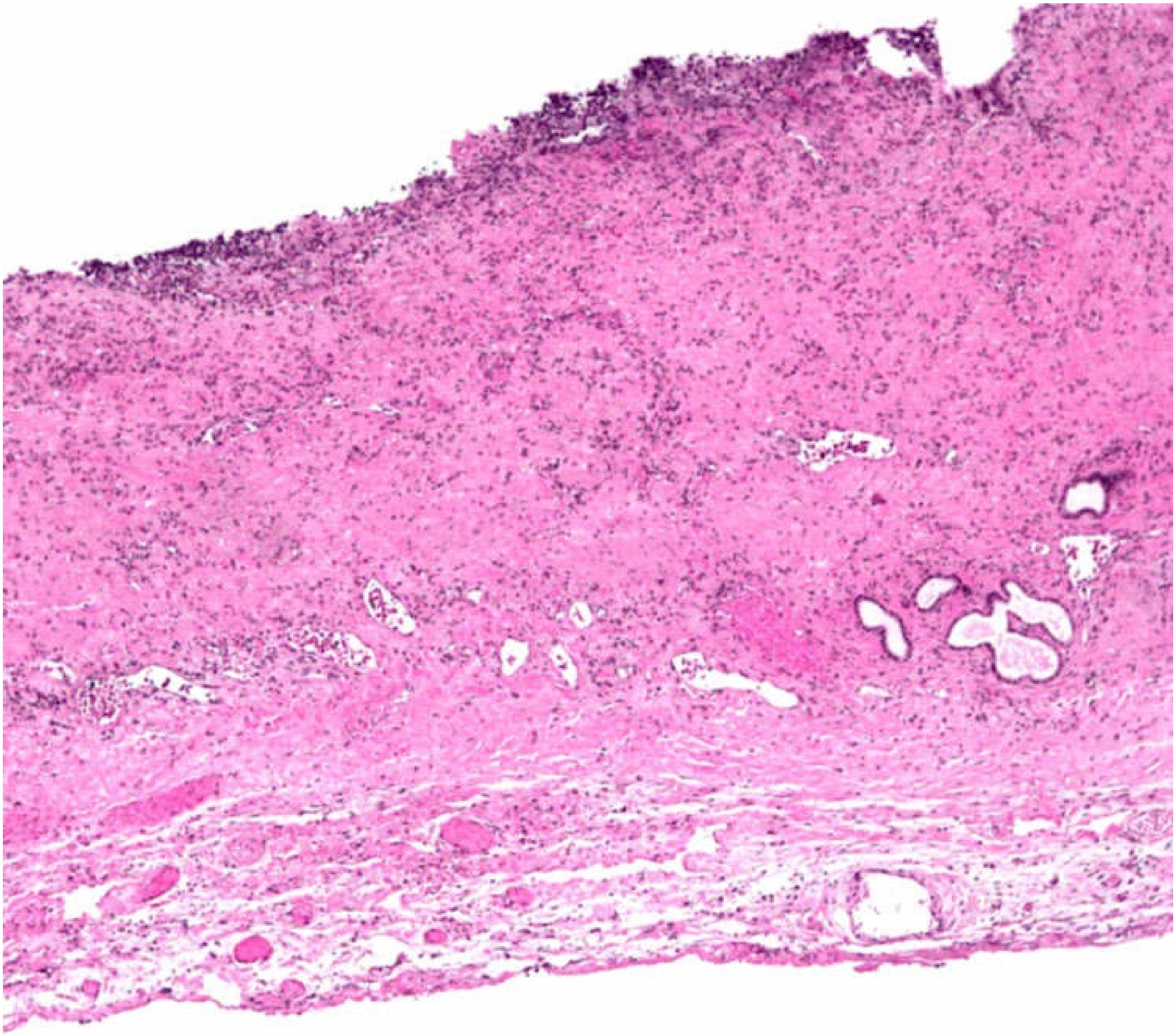
- May be clinically and histologically (on liver biopsy) difficult to distinguish from choledochal cyst in infants
- Radiographic studies required

Other Causes of Biliary Obstruction

- Changes on liver biopsy often similar
- Imaging required to detect choledochal cyst



This section of a choledochal cyst shows a fibrotic wall with acute and chronic inflammation and intact overlying biliary epithelium.



This section of choledochal cyst from a resection specimen shows a thickened fibrotic wall with acute and chronic inflammation and ulcerated overlying epithelium.

SELECTED REFERENCES

1. Machado, NO, et al. Choledochal cyst in adults: etiopathogenesis, presentation, management, and outcome-case series and review. *Gastroenterol Res Pract*. 2015; 2015:602591.
2. Soares, KC, et al. Presentation and clinical outcomes of choledochal cysts in children and adults: a multi-institutional analysis. *JAMA Surg*. 2015; 150(6):577–584.
3. Katabi, N, et al. Choledochal cysts: a clinicopathologic study of 36 cases with emphasis on the morphologic and the immunohistochemical features of premalignant and malignant alterations. *Hum Pathol*. 2014; 45(10):2107–2114.
7. Todani, T, et al. Congenital bile duct cysts: classification, operative procedures, and review of

thirty-seven cases including cancer arising from choledochal cyst. *Am J Surg*. 1977; 134(2):263–269.

4. Soares, KC, et al. Choledochal cysts: presentation, clinical differentiation, and management. *J Am Coll Surg*. 2014; 219(6):1167–1180.
5. Chaudhary, A, et al. Choledochal cysts–differences in children and adults. *Br J Surg*. 1996; 83(2):186–188.
6. Yamaguchi, M. Congenital choledochal cyst. Analysis of 1,433 patients in the Japanese literature. *Am J Surg*. 1980; 140(5):653–657.

SECTION 2

INFLAMMATORY DISORDERS OF THE GALLBLADDER AND EXTRAHEPATIC BILIARY TREE

OUTLINE

Cholelithiasis

KEY FACTS

Terminology

- Formation of stones in gallbladder
  - One of most common gastrointestinal diseases worldwide
  - – Particularly common in Scandinavia, Chile
  - – In United States, estimated 10-20% of population have gallstones
- 2 main types: Cholesterol stones and pigment stones
  - Cholesterol stones
    - – > 80% of stones in developed nations
  - Pigment stones
    - – Black: Associated with hemolytic disorders, cirrhosis, TPN
    - – Brown: Associated with ascending cholangitis and biliary inflammation

Clinical Issues

- Most gallstones are clinically silent
  - May present with right upper quadrant pain, intolerance of fatty food
- 2-4 times more common in women than men
- Laparoscopic cholecystectomy is standard therapy

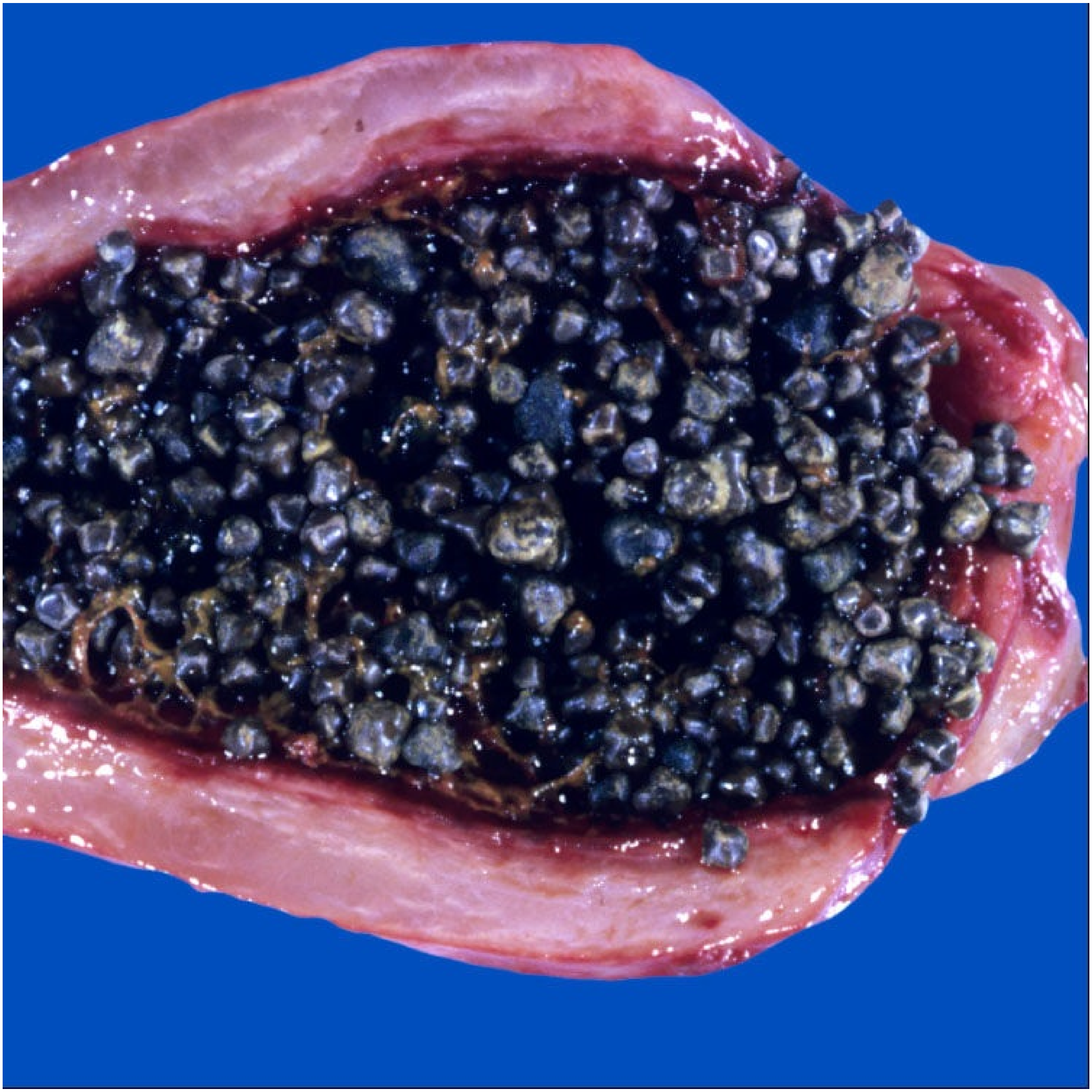
Imaging

- Ultrasound (diagnostic modality of choice) can detect stones > 3 mm in diameter

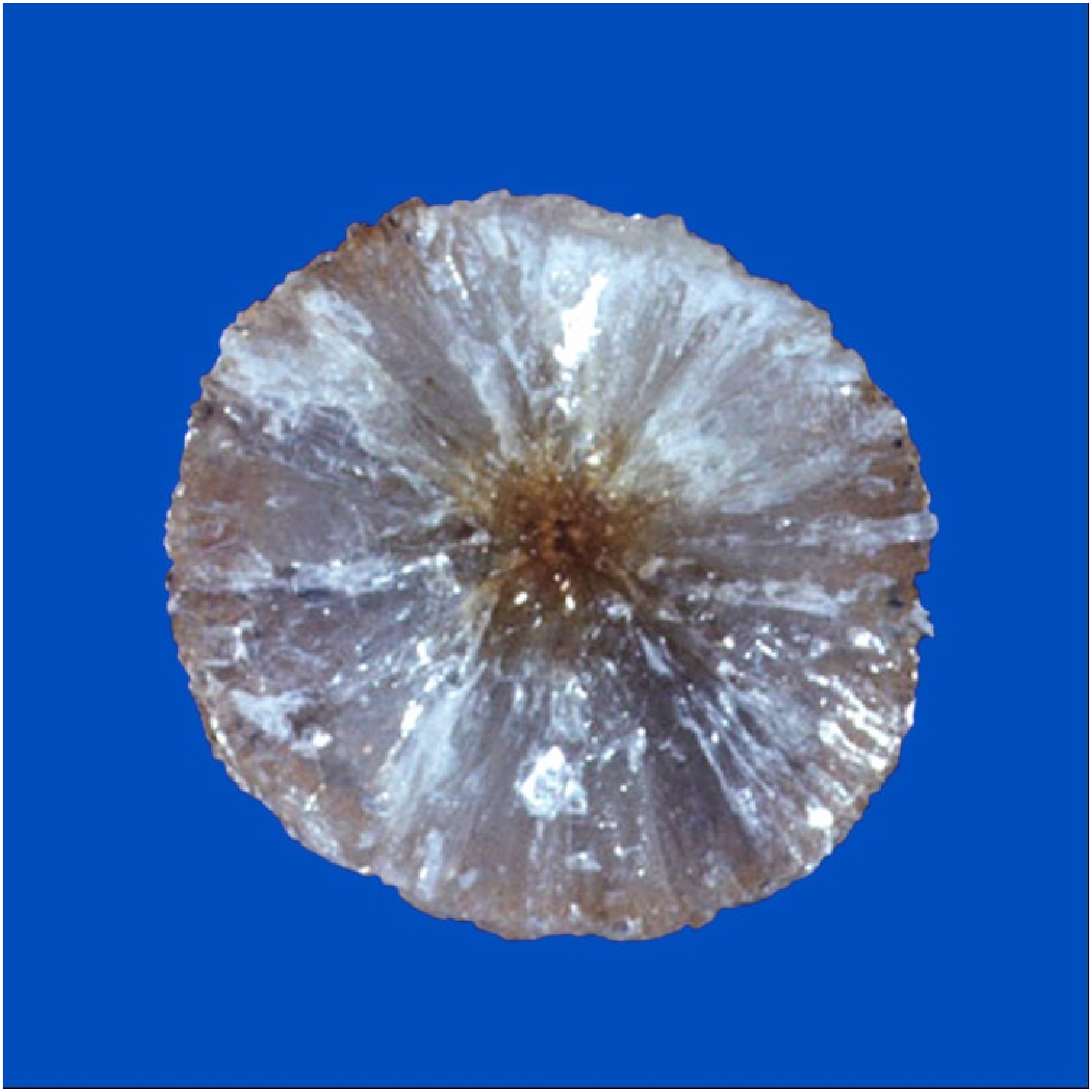
Macroscopic

- Cholesterol stones usually < 2 cm, multiple, and round or faceted
- Black pigment stones are 2-5 mm, shiny, irregular, multifaceted
- Brown pigment stones have softer texture and flaky appearance, often larger than black stones
- Stones are often associated with inflammation (cholecystitis)

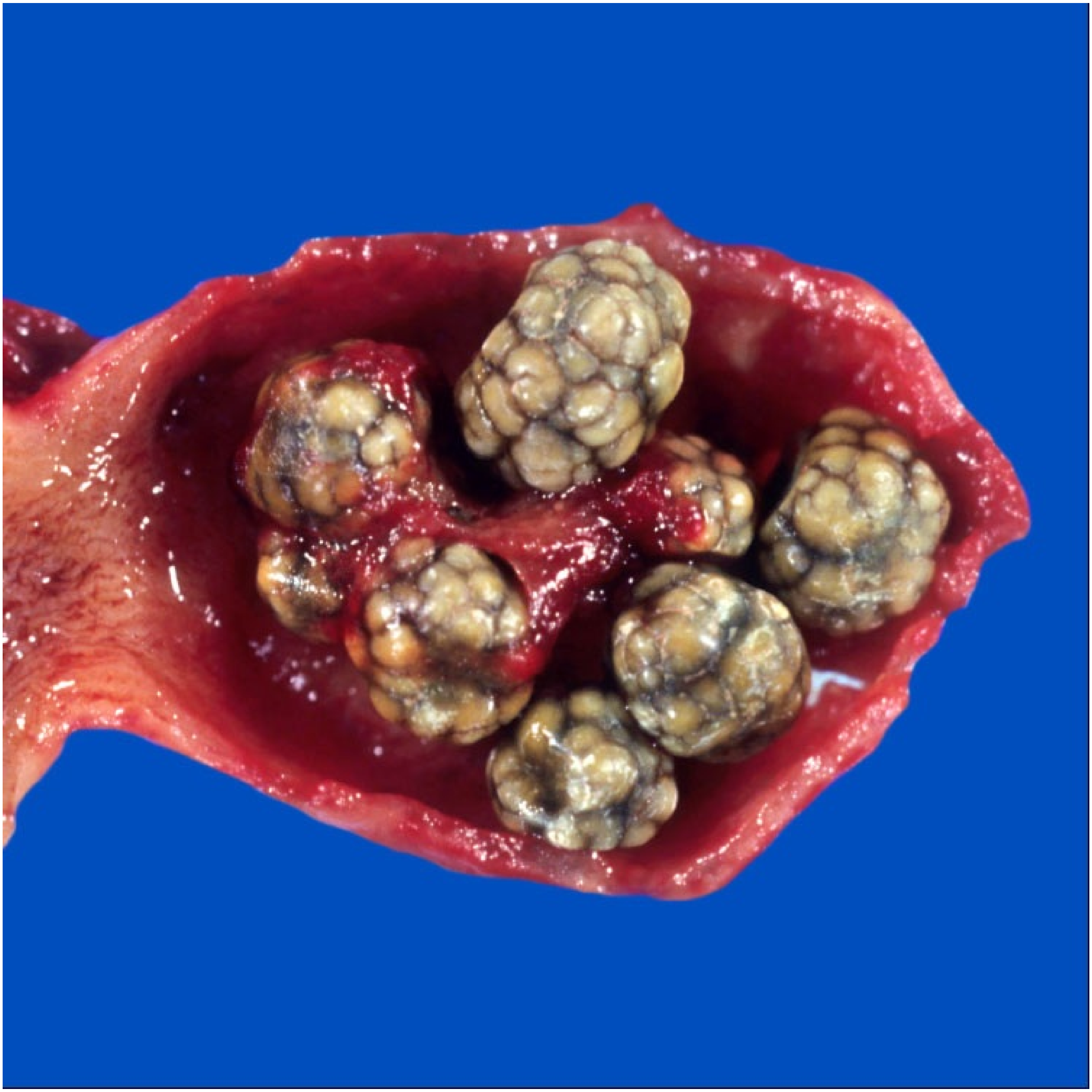
Cholesterol Gallstones
This gallbladder is filled with numerous smooth yellow mixed cholesterol stones. The gallbladder wall is mildly thickened and hyperemic, indicative of cholecystitis. (Courtesy G. F. Gray, MD.)



Black Pigment Gallstones
This gallbladder contains numerous faceted black pigment stones that distend the gallbladder lumen. The gallbladder wall is thickened and edematous due to associated chronic cholecystitis. (Courtesy G. F. Gray, MD.)



Cholesterol Stone, Cut Surface
The cut surface of this large gallstone shows a radial arrangement of cholesterol crystals around a central pigmented core.



Cholesterol Stones
Lobulated cholesterol stones, some of which appear partially intramural, are seen within a hyperemic gallbladder. (Courtesy G. F. Gray, MD.)

TERMINOLOGY

Definitions

• Formation of stones in gallbladder

ETIOLOGY/PATHOGENESIS

Cholesterol Stone Formation

- > 80% of stones in developed nations are mixed cholesterol stones
  - Bile supersaturation, destabilization plus gallbladder hypermotility
  - Formation of cholesterol crystals, which grow and aggregate with mucin proteins to form stones
  - Also contain variable amounts of calcium bilirubinate, calcium carbonate
  - Numerous risk factors
    - Obesity, multiparity, rapid weight loss, estrogen replacement therapy, oral contraceptive use, hypertriglyceridemia, many medications
    - Higher rates in Latin American women (Hispanic Americans) and Native Americans in both North and South America

Black Pigment Stones

- Contain calcium bilirubinate, calcium phosphate, and calcium carbonate
- Associated with hemolytic disorders, cirrhosis, malaria, TPN, Crohn disease

Brown Pigment Stones

- Calcium salts of bilirubin and palmitate, more cholesterol than black stones
- Strongly associated with ascending cholangitis and biliary inflammation, especially due to *Escherichia coli* and flukes

CLINICAL ISSUES

Epidemiology

- Incidence
  - One of most common gastrointestinal diseases worldwide
    - Variable in different parts of world
      - Particularly common in Scandinavia, Chile
      - In United States, estimated 10-20% of population have gallstones
      - Pigment stones are much more common in Asian and African populations
- Age
  - Overall, increased incidence with age; quite uncommon in children
- Sex
  - 2-4 times higher in women than men

Presentation

- Majority of gallstones are clinically silent
- Symptoms usually consist of right upper quadrant pain, flatulence, and intolerance of fatty food
- Complications include acute and chronic cholecystitis, choledocholithiasis, fistulas, acute pancreatitis, and gallbladder cancer

Treatment

- Laparoscopic cholecystectomy most common treatment
  - Approach to asymptomatic gallstones remains controversial
  - Incidence of carcinoma < 1%, so cholecystectomy not routinely recommended

IMAGING

Radiographic Findings

- 70-90% of gallstones are radiolucent; at least 80% of these are cholesterol stones
- Black stones may be radiopaque
- Ultrasound (diagnostic modality of choice) can detect stones > 3 mm in diameter

MACROSCOPIC

Cholesterol Stones

- Usually < 2 cm, multiple, and round or faceted
  - Cut surface is laminated with alternating layers having variegated appearance depending on how much pigment is present
  - Stones with > 90% cholesterol are referred to as pure cholesterol stones
  - Round or ovoid, single, usually 2-4 cm in diameter
  - Cut surface shows radial arrangement of crystals; pigment is either absent or present only in scant amounts

Pigment Stones

- Black pigment stones
  - 2-5 mm, shiny, irregular, multifaceted
- Brown pigment stones
  - Softer texture and flaky appearance, often larger than black stones

Unusual Types of Gallstones

- Disappearing gallstones
  - 3 possible mechanisms: Spontaneous passage via common bile duct, passage through cholecystoenteric fistula, and spontaneous dissolution
- Intramural gallstones
  - Stones become adherent to wall, leading to ulceration and erosion into muscularis
  - May form within Rokitansky-Aschoff sinuses
- Gas-containing gallstones
  - Nitrogen, smaller amounts of carbon dioxide and oxygen

SELECTED REFERENCES

1. Qiao, T, et al. The systematic classification of gallbladder stones. *PLoS One*. 2013; 8(10):e74887.

2.Vítek, L, et al. New pathophysiological concepts underlying pathogenesis of pigment gallstones. *Clin Res Hepatol Gastroenterol*. 2012; 36(2):122–129.
3.Dowling, RH. Review: pathogenesis of gallstones. *Aliment Pharmacol Ther*. 2000; 14(Suppl 2):39–47.
4.Johnston, DE, et al. Pathogenesis and treatment of gallstones. *N Engl J Med*. 1993; 328(6):412–421.
5.Moser, AJ, et al. The pathogenesis of gallstone formation. *Adv Surg*. 1993; 26:357–386.
6.Bowen, JC, et al. Gallstone disease. Pathophysiology, epidemiology, natural history, and treatment options. *Med Clin North Am*. 1992; 76(5):1143–1157.
7.Paumgartner, G, et al. Gallstones: pathogenesis. *Lancet*. 1991; 338(8775):1117–1121.

Acute Cholecystitis

KEY FACTS

Etiology/Pathogenesis

- Acute **calculous** cholecystitis: 95% of cases
- Obstruction of cystic duct by pigment or cholesterol stones
- Acute **acalculous** cholecystitis: 5% of cases
- Risk factors include critical illness, burns, trauma, major surgical procedures, diabetes, immunosuppression

Clinical Issues

- Right upper quadrant pain, tenderness, and guarding
- Fever, leukocytosis
- Laparoscopic cholecystectomy is procedure of choice

Macroscopic

- Mural thickening, congestion, purulent exudate, adhesions

Microscopic

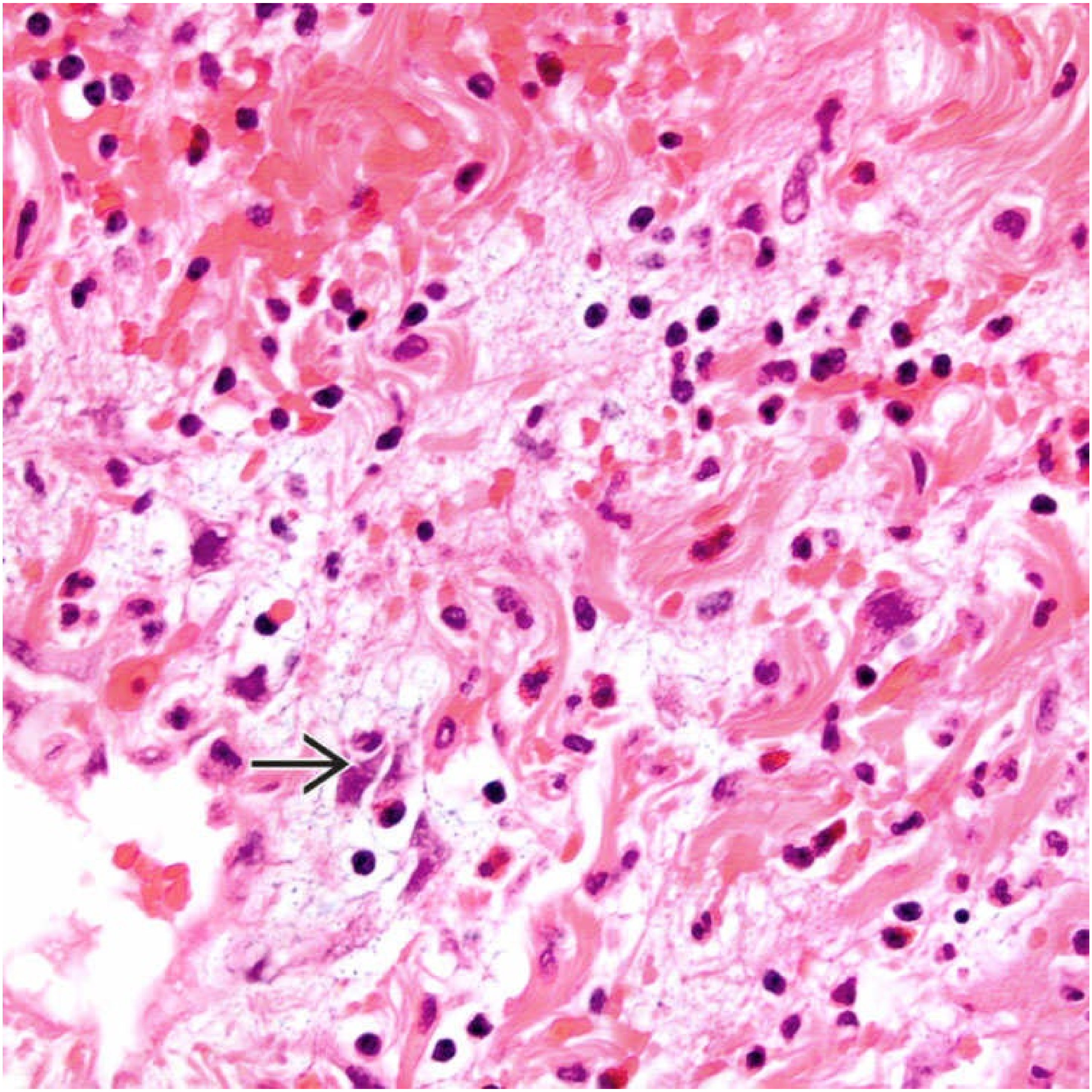
- Changes depend on duration of disease
  - Inflammation may be sparse in early disease
  - Edema and congestion seen in early disease
- Inflammation dominated by neutrophils and variable necrosis in later stages of disease
- Widespread fibroblastic proliferation can occur
- Transmural fibrosis and Rokitansky-Aschoff (RA) sinuses, stigmata of chronic cholecystitis, may be present
- Variant forms
  - Xanthogranulomatous: Foamy macrophages as a result of response to bile due from ruptured RA sinuses
  - Emphysematous: Necrotic wall with gas bubbles and often contains gram(+) bacilli
  - Eosinophilic: Eosinophils comprise > 90% of infiltrate; may be associated with parasites,

hypereosinophilic syndrome

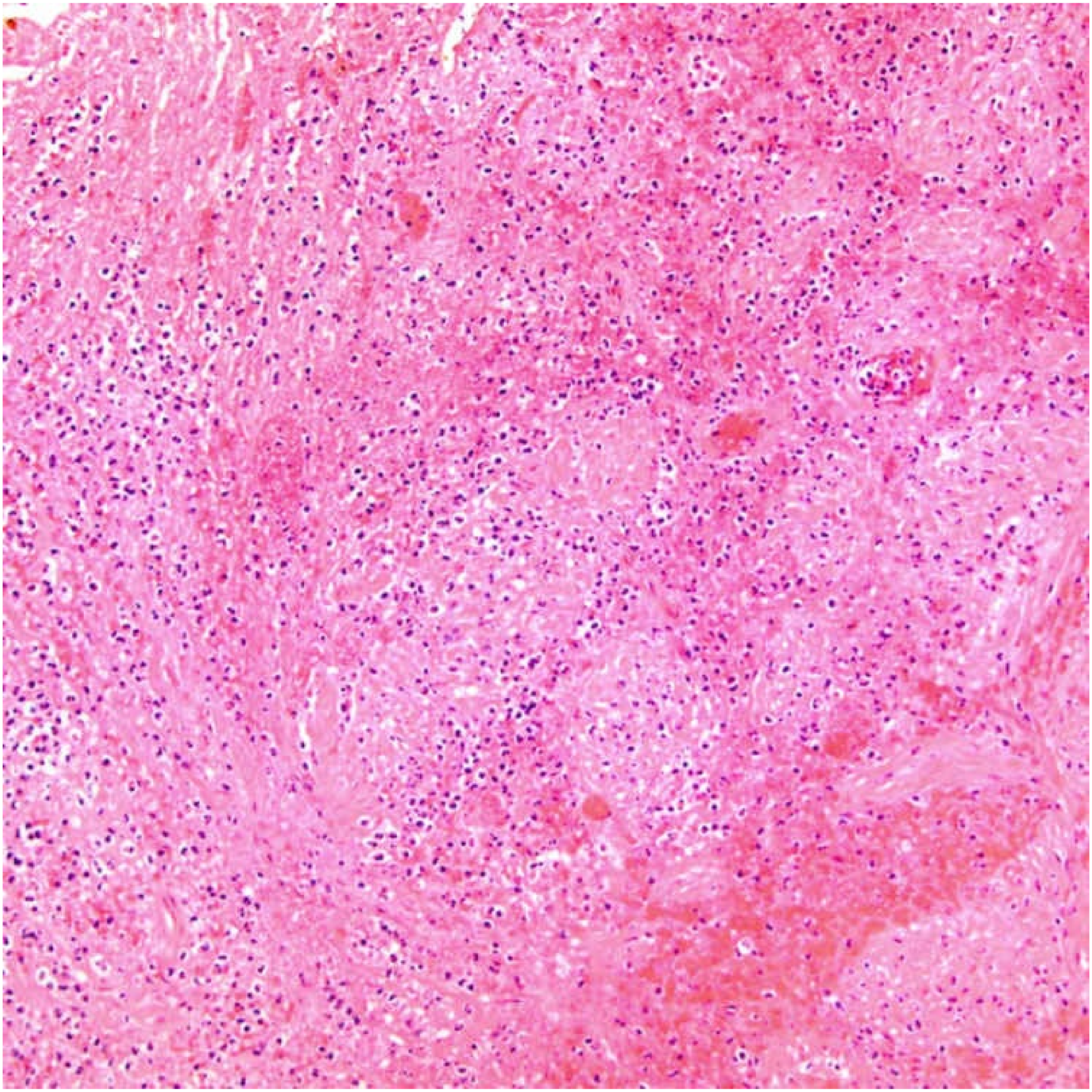
Top Differential Diagnoses

- Chronic cholecystitis
- Dysplasia or carcinoma

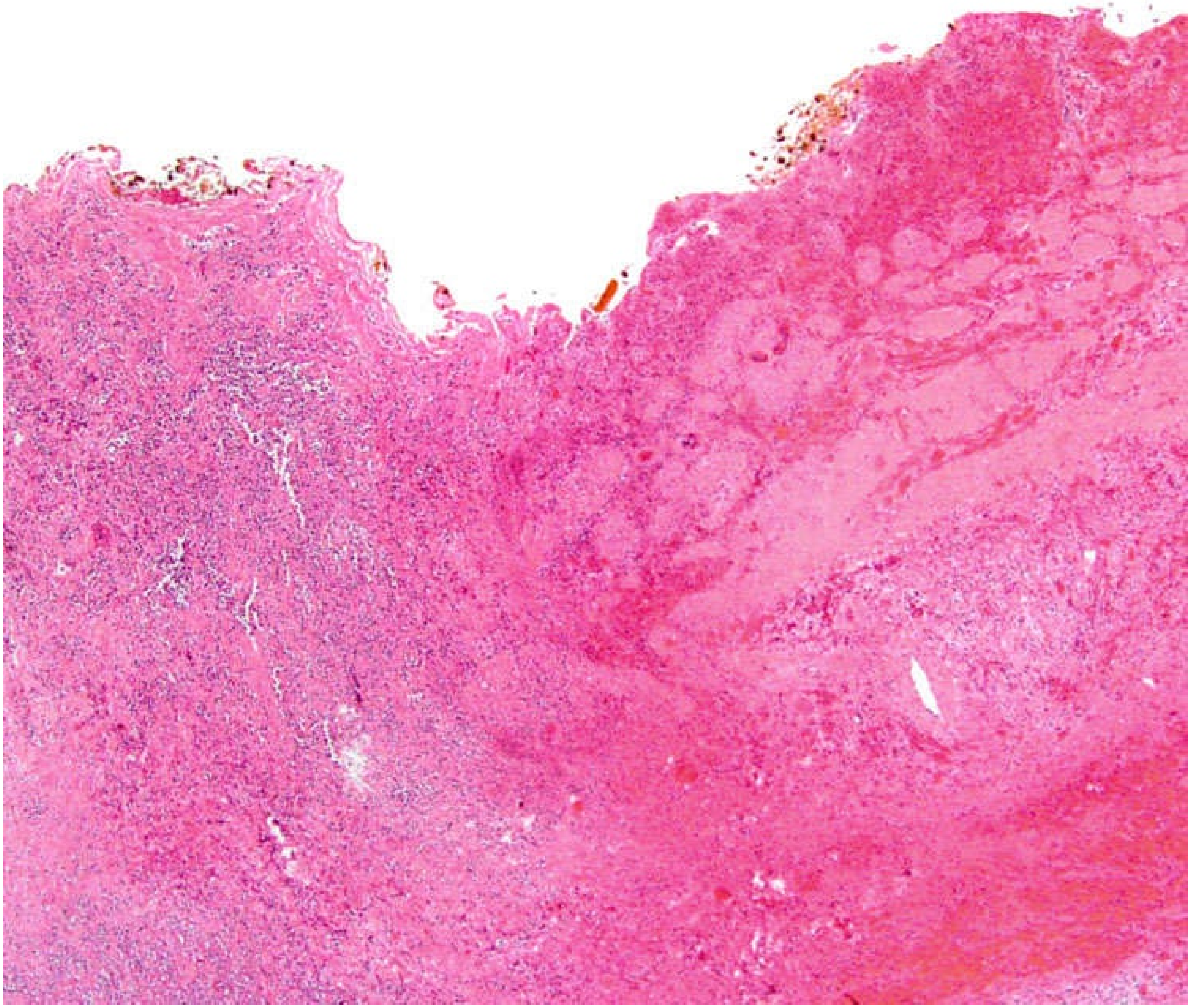
Thickened Wall
The thickened wall and congested mucosa suggest acute cholecystitis in this gallbladder. The gallstone ⇨ impacted in the neck of the gallbladder was the etiology of acute cholecystitis.



Early Changes
Early acute cholecystitis may show marked edema and hemorrhage but minimal inflammation. Dilation of capillaries and lymphatics can occur. Also note the reactive fibroblasts →.



Acute Inflammatory Exudate
A case of severe acute cholecystitis shows mural necrosis, fresh hemorrhage, and a prominent neutrophilic exudate.



Transmural Necrosis
Diffuse ulceration, fresh hemorrhage, and full thickness necrosis of the muscularis propria are characteristic of acute cholecystitis. The term necrotizing cholecystitis has been used to describe this phase of the disease.

TERMINOLOGY

Definitions

- Acute inflammation of gallbladder

ETIOLOGY/PATHOGENESIS

Acute Calculous Cholecystitis

- Key elements are obstruction of cystic duct by stones and bile supersaturated with cholesterol
  - Trauma to mucosa releases phospholipase from lysosomes
  - Phospholipase converts lecithin in bile to lysolecithin, which damages gallbladder epithelium
- Secondary bacterial infection with enteric organisms occurs in 20% of cases
- Overgrowth by gas-producing organisms leads to emphysematous cholecystitis

Acute Acalculous Cholecystitis

- Accounts for 5% of cases
  - Risk factors
  - Critical illness, burns, trauma, major surgical procedures, diabetes, immunosuppression
  - Common elements in this group of disorders are biliary sludge formation and mucosal ischemia

CLINICAL ISSUES

Epidemiology

- Age
  - Commonly seen between 40-80 years
- Sex
  - F > M

Presentation

- Right upper quadrant pain, tenderness, and guarding
- Fever, leukocytosis
- Murphy sign: Arrest of inspiration while palpating gallbladder during deep inspiration

Treatment

- Surgical approaches
  - Early laparoscopic cholecystectomy is treatment of choice
  - Conservative measures reserved for poor surgical candidates
  - Percutaneous cholecystostomy may be performed

Prognosis

- Acute acalculous cholecystitis, unlike acute calculous cholecystitis, is associated with high mortality

Complications

- Gangrenous cholecystitis
  - Perforation
  - Emphysematous cholecystitis
  - Caused by overgrowth by gas-producing organisms

- Empyema of gallbladder

IMAGING

Ultrasonographic Findings

- Gallstones in 95% of cases
- Thickening of gallbladder (5 mm or more), pericholecystic fluid, ultrasonographic Murphy sign

Hepatobiliary Scintigraphy

- Absence of gallbladder filling within 60 minutes after tracer administration indicates acute cholecystitis

MACROSCOPIC

General Features

- Thickened congested wall, may appear necrotic
- Serosa dull, occasionally with fibrinopurulent exudates
- Mucosal edema and ulceration; pus may be present
- 95% have stones
- Serosal adhesions

MICROSCOPIC

Histologic Features

- Changes depend on duration of disease
  - Edema, congestion, and hemorrhage in early disease
    - May lack inflammation altogether
- Inflammatory infiltrate
  - Acute inflammation with neutrophil predominance
  - Eosinophils, macrophages, and lymphocytes appear later
  - Eventually transmural inflammation, secondary vasculitis, and mural necrosis develop
- Fibroblastic proliferation with tissue culture-like look
- Mucosal ulceration
- Transmural fibrosis and Rokitansky-Aschoff (RA) sinuses, stigmata of chronic cholecystitis, may be present
- Calculous and noncalculous forms are histologically similar
- Variant forms
  - Xanthogranulomatous: Foamy macrophages as result of response to bile due from ruptured RA sinuses
  - Emphysematous: Necrotic wall with gas bubbles and often contains gram(+) bacilli
  - Eosinophilic: Eosinophils comprise > 90% of infiltrate; may be associated with parasites, hypereosinophilic syndrome

DIFFERENTIAL DIAGNOSIS

Chronic Cholecystitis

- Lacks acute inflammation, fibroblastic proliferation, edema/congestion

Gallbladder Dysplasia and Carcinoma

- Cytoarchitectural atypia separates neoplasia from regenerative changes
- Ulceration and inflammation can be seen on both regenerative and reactive settings

SELECTED REFERENCES

1. Elwood, DR. Cholecystitis. *Surg Clin North Am*. 2008; 88(6):1241–1252. [viii].
2. Strasberg, SM. Clinical practice. Acute calculous cholecystitis. *N Engl J Med*. 2008 Jun 26; 358(26):2804–2811. [Review. Erratum in: N Engl J Med. 359(3):325,2008].
3. Laurila, JJ, et al. Histopathology of acute acalculous cholecystitis in critically ill patients. *Histopathology*. 2005; 47(5):485–492.
4. Babb, RR. Acute acalculous cholecystitis. A review. *J Clin Gastroenterol*. 1992; 15(3):238–241.

Chronic Cholecystitis

KEY FACTS

Etiology/Pathogenesis

- Almost always associated with gallstones
  - Radiolucent cholesterol stones
  - Risk factors: Old age, female sex, obesity, hyperlipidemia
  - Radiopaque pigment stones
  - Risk factors: Chronic hemolysis, biliary infection, and gastrointestinal diseases affecting bile salt reabsorption

Clinical Issues

- More common in women; ~ 3:1

Microscopic

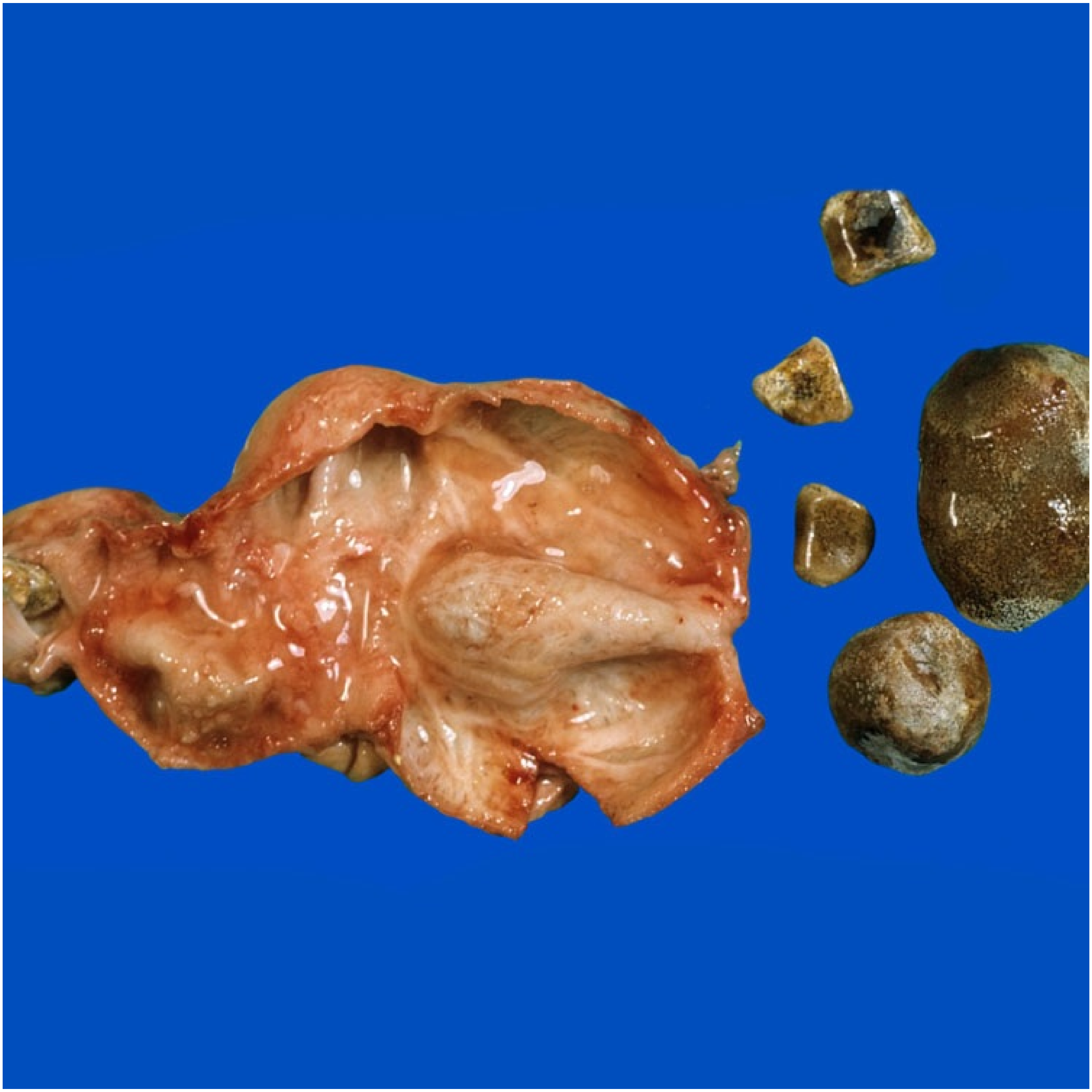
- Predominantly mononuclear inflammatory infiltrate with lymphocytes dominating over plasma cells and histiocytes
  - Minor component of eosinophils and neutrophils may be present
  - Wall thickening secondary to muscular hypertrophy and fibrosis
  - Metaplastic changes; most common is antral type
  - Rokitansky-Aschoff sinuses
  - Histologic variants
  - Follicular cholecystitis: Prominent lymphoid follicles
  - Lymphoplasmacytic sclerosing cholecystitis (IgG4-related): Often associated with autoimmune pancreatitis
  - Eosinophilic cholecystitis: > 90% of infiltrate composed of eosinophils

Top Differential Diagnoses

- Normal gallbladder
- Acute cholecystitis

Diagnostic Checklist

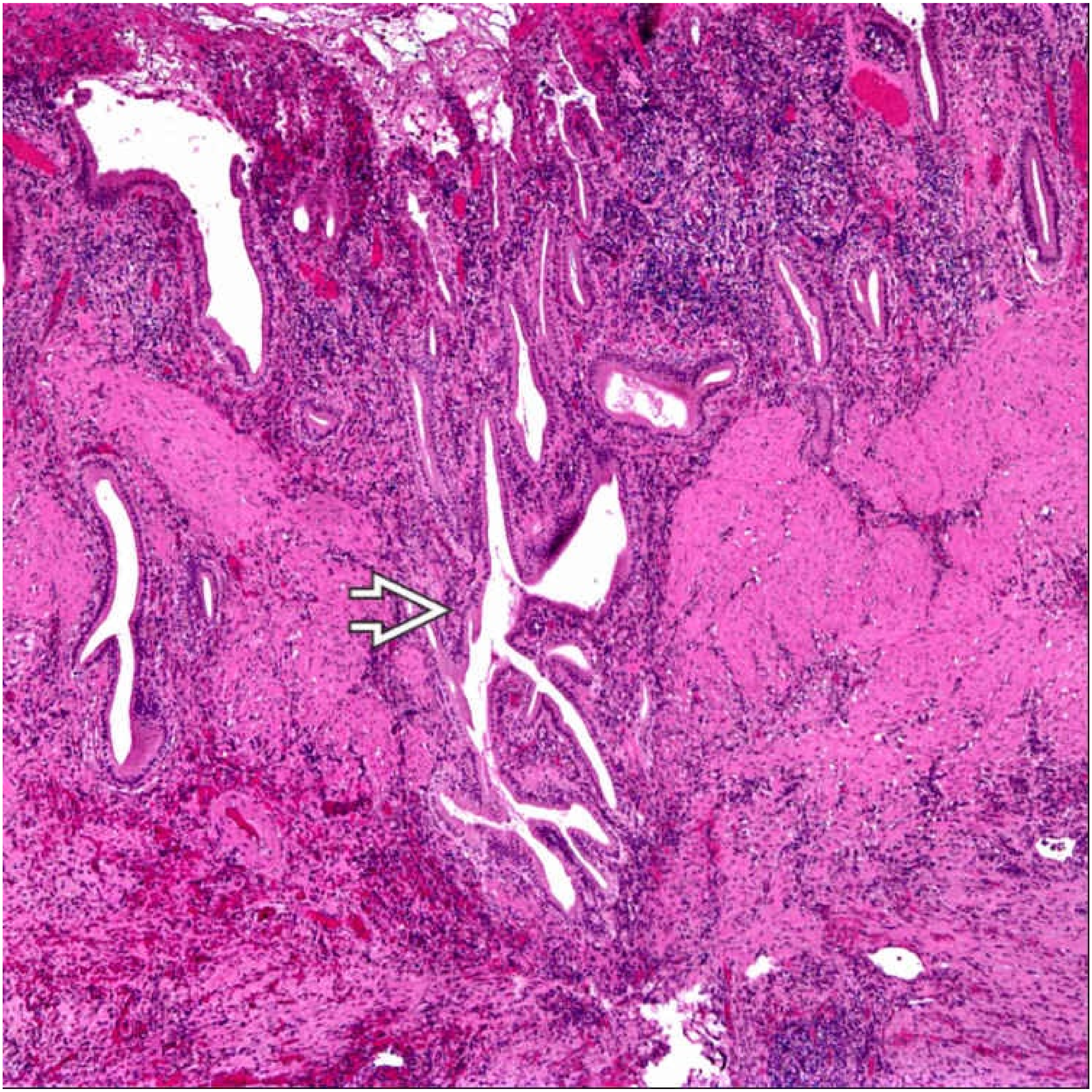
- Presence of gallstones is neither necessary nor sufficient for diagnosis of chronic cholecystitis



Gallstones
Gallbladder with multiple mixed stones is shown. Most chronic cholecystitis cases are associated with stones; however, symptomatic stones can be present in histologically normal gallbladder.

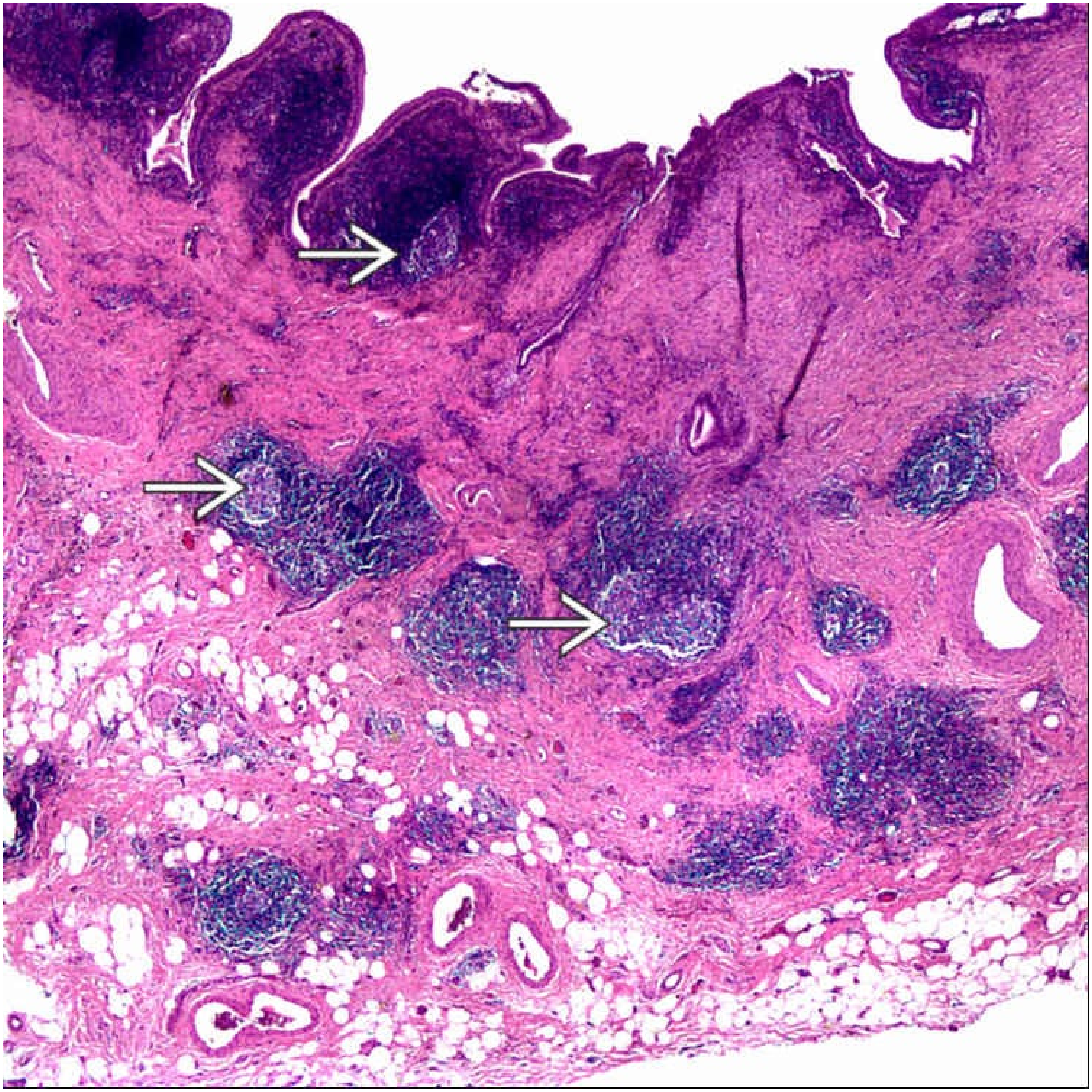
Porcelain Gallbladder

Thick, fibrotic gallbladder shows dystrophic calcification ⇨ reminiscent of porcelain. This variant is associated with an increased risk of adenocarcinoma.



Rokitansky-Aschoff Sinuses

The mucosa herniates through the muscularis propria, resulting in Rokitansky-Aschoff sinuses ⇨. This is a common finding in chronic cholecystitis, but is not sufficient for the diagnosis by itself.



Follicular Cholecystitis
Multiple lymphoid follicles are shown with germinal centers in the gallbladder mucosa and wall ⇒. In some cases, these follicles can have a polypoid appearance on gross examination.

TERMINOLOGY

Definitions

• Chronic inflammation of gallbladder

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Almost always associated with gallstones
  - Cholesterol stones (80% in West): Supersaturation of bile with cholesterol
  - – Risk factors: Old age, female sex, obesity, hyperlipidemia
- Pigment stones composed of bilirubin calcium salts
- – Risk factors: Chronic hemolysis, biliary infection, and gastrointestinal diseases affecting bile salt reabsorption
- Pure cholesterol stones are radiolucent, whereas pigment stones are radiopaque

CLINICAL ISSUES

Epidemiology

- Age
  - 40s or 50s
- Sex
  - More common in women (3:1)

Presentation

- Episodic, steady, abdominal pain (“biliary colic”)
  - Usually located in epigastrium or right upper quadrant
  - May be precipitated by ingestion of food

Treatment

- Cholecystectomy is curative

IMAGING

Ultrasonographic Findings

- Demonstrate stones and abnormalities in gallbladder wall

MACROSCOPIC

General Features

- Variable, depending on degree of inflammation and fibrosis
  - Normal or mild wall thickening and serosal adhesions
  - Shrunken with marked wall thickening and scarring

- Mucosa may be flattened, granular, ulcerated, or polypoid

MICROSCOPIC

Histologic Features

- Inflammation
  - Predominantly lymphocytic infiltrate
  - Focal or diffuse in lamina propria, may extend into muscularis and pericholecystic tissues
  - Minor component of eosinophils and neutrophils
- Wall thickening
  - Secondary to muscular hypertrophy and fibrosis
  - Adventitia is frequently thickened with diffuse scarring
- Metaplastic changes
  - Gastric (pyloric/antral or foveolar type)
  - Intestinal metaplasia, rarely squamous
- Rokitansky-Aschoff sinuses
  - Herniation of mucosa into or through muscularis
  - Indicative of increased intraluminal pressure or outflow obstruction
  - Commonly associated with hypertrophic muscularis
  - Not sufficient for diagnosis by itself
- Variants
  - Follicular cholecystitis
    - Numerous lymphoid follicles with germinal centers
    - Large follicles can appear as polyps
    - May occur with infections (especially gram-negative) and primary sclerosing cholangitis
  - Chronic acalculous cholecystitis
    - No gallstones
    - Variant with diffuse lymphoplasmacytic infiltrate confined to lamina propria may be associated with extrahepatic bile duct obstruction
  - Porcelain gallbladder
    - Dystrophic calcification imparting eggshell gross appearance
    - Associated with higher risk of carcinoma
  - Lymphoplasmacytic sclerosing cholecystitis (IgG4-related)
    - Often associated with autoimmune pancreatitis
    - Dense lymphoplasmacytic infiltrate, often with eosinophils and prominent extramural involvement
    - Phlebitis and inflammatory pseudotumor-like nodules
    - Increased IgG4(+) plasma cells on immunohistochemistry (typically > 10 per HPF)
    - Increased IgG4 to IgG ratio on immunohistochemistry (typically 0.47 or higher)
  - Eosinophilic cholecystitis
    - Rare entity with eosinophils comprising > 90% of inflammatory cells
    - Often idiopathic, but has been associated with hypereosinophilic syndrome, adverse drug reaction, allergies, systemic vasculitides, and parasitic infestation
    - Should be distinguished from Langerhans cell histiocytosis

DIFFERENTIAL DIAGNOSIS

Normal Gallbladder

- Sparse, focally distributed lymphoid cells
- Lacks fibrosis, Rokitansky-Aschoff sinuses

Acute Cholecystitis

- Acute inflammation, edema, hemorrhage

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Gallstones are not necessary nor sufficient for diagnosis
- Normal gallbladder contains some chronic inflammatory cells
- Gallbladder with symptomatic calculi can be histologically normal

SELECTED REFERENCES

1. Wang, WL, et al. Autoimmune pancreatitis-related cholecystitis: a morphologically and immunologically distinctive form of lymphoplasmacytic sclerosing cholecystitis. *Histopathology*. 2009; 54(7):829–836.
2. Elwood, DR. Cholecystitis. *Surg Clin North Am*. 2008; 88(6):1241–1252. [viii].
3. Shakov, R, et al. Eosinophilic cholecystitis, with a review of the literature. *Ann Clin Lab Sci*. 2007; 37(2):182–185.
4. Halpert, B. Significance of the Rokitansky-Aschoff sinuses. *Am J Gastroenterol*. 1961; 36:534–539.
5. Edulund, Y, et al. Histopathology of the gallbladder in gallstone disease related to clinical data; with a proposal for uniform surgical and clinical terminology. *Acta Chir Scand*. 1959; 116(5-6):450–460.

Xanthogranulomatous Cholecystitis

KEY FACTS

Terminology

- Variant of chronic cholecystitis featuring florid proliferation of foamy macrophages and granulomatous reaction to bile
  - a.k.a. cholegranulomas or cholecystic granulomas

Etiology/Pathogenesis

- Usually preceded by rupture of Rokitansky-Aschoff sinus
  - Bile and lipid extruded into gallbladder wall, producing granulomatous reaction

Clinical Issues

- 4-9% of cholecystectomy specimens
  - Majority of cases associated with gallstones
- Rarely, inflammation extends from gallbladder to other organs to form adhesions or fistulas

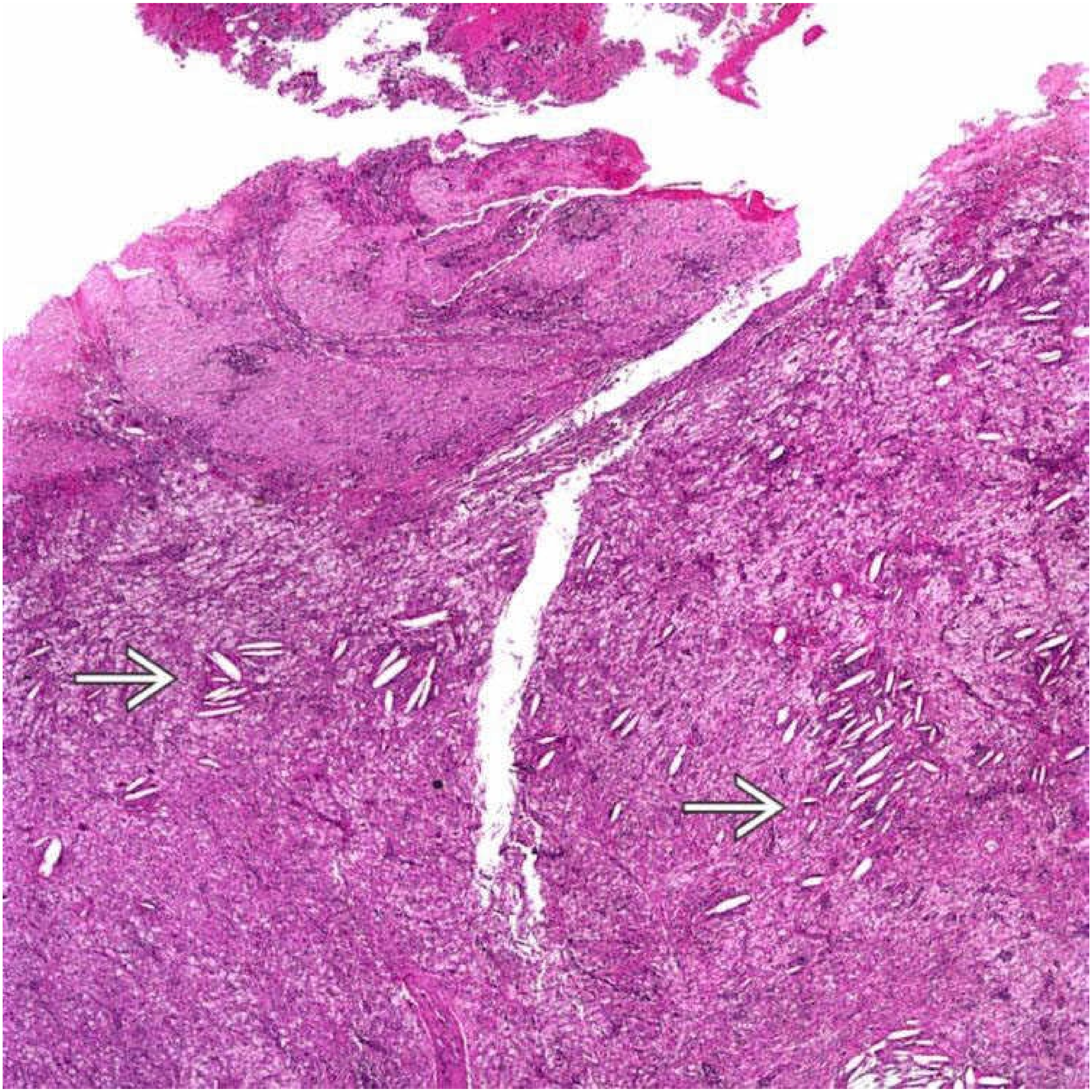
Macroscopic

- Cream to brown tumor-like masses, nodules, or plaques
  - Usually intramural, typically multiple
  - Poorly circumscribed and soft
  - Range from few millimeters up to 3 cm
- Gallbladder wall often markedly thickened (up to 2 cm)
  - May mimic malignancy both grossly and radiographically

Microscopic

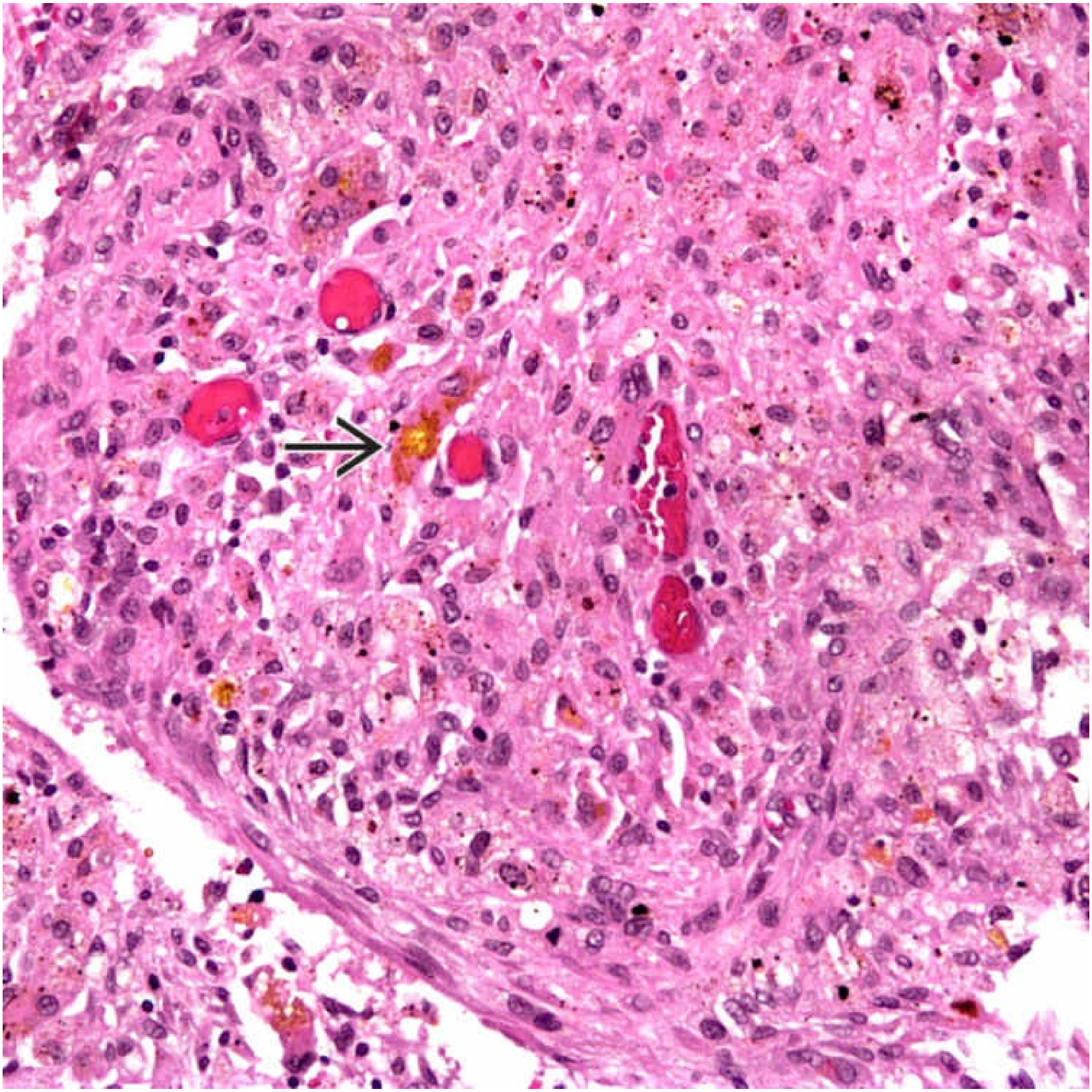
- Spectrum of granulomatous lesions centered on ruptured Rokitansky-Aschoff sinuses
  - Range of lesions from loose aggregates of foamy histiocytes to granulomas
  - Associated ceroid pigment, bile, cholesterol clefts

• Pools of extravasated bile may be present in wall of gallbladder
• Multinucleated giant cells common
• Over time, organization occurs, and fibrosis may predominate, further mimicking malignancy

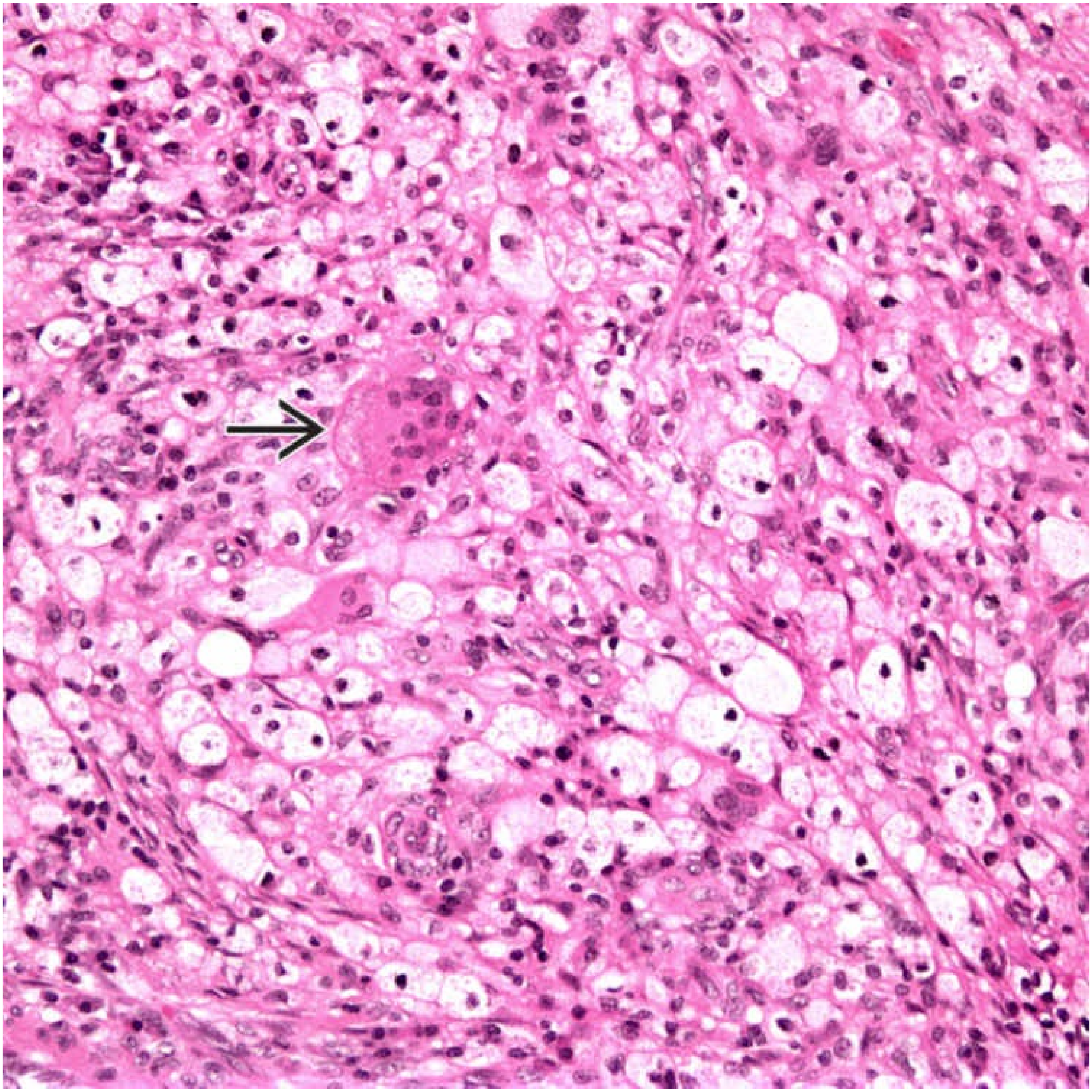


Thickened Wall and Mucosal Ulceration

This low-power view shows thickening of the wall, mucosal ulceration, and a proliferation of foamy macrophages. Note the cholesterol clefts ⇒ as well, which are abundant within the foamy macrophage infiltrate.

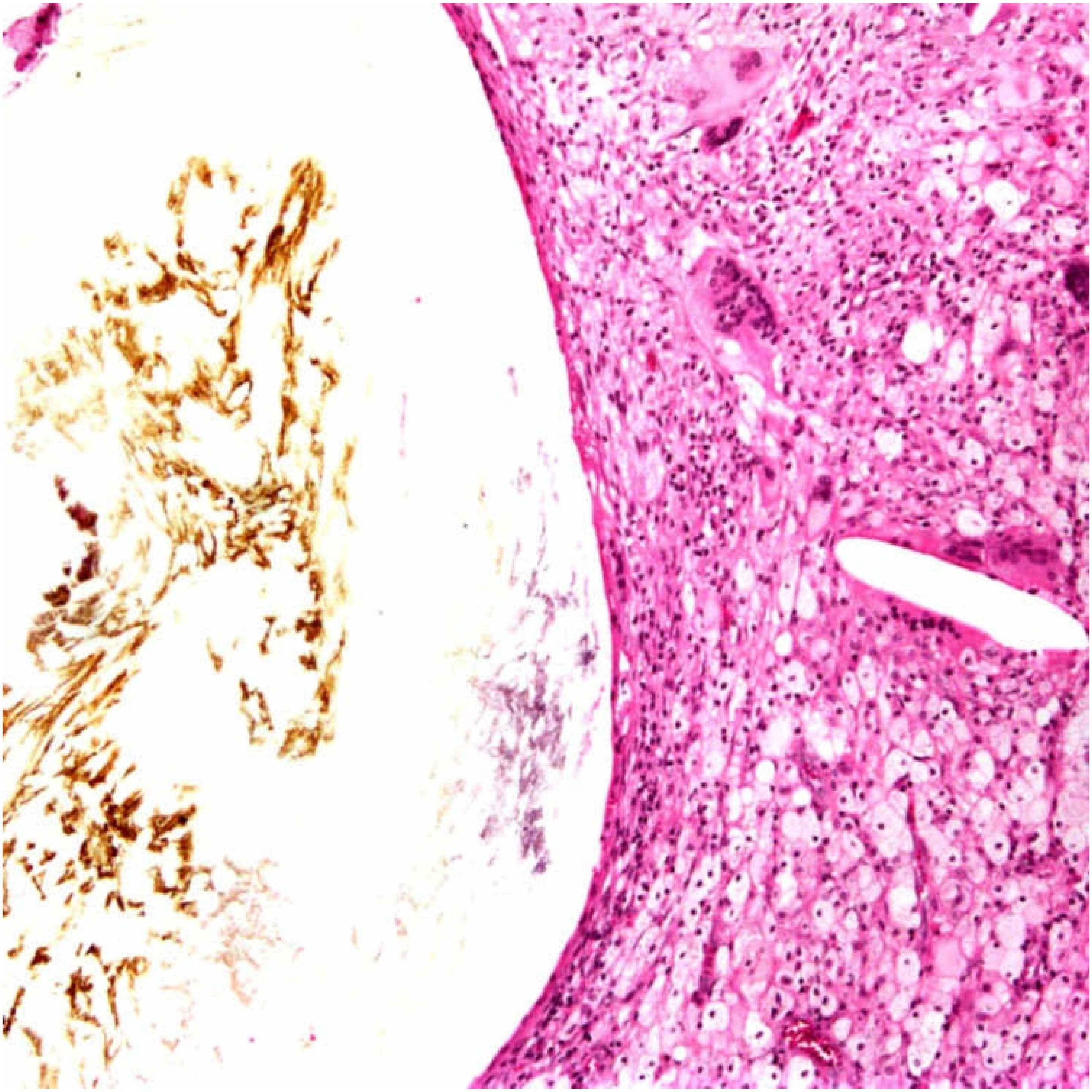


Nodular Macrophage Infiltrate
This nodular collection of macrophages in the wall of the gallbladder contains bile → and ceroid-laden histiocytes.



Foamy Histiocytes

Xanthogranulomatous cholecystitis is often characterized by a dense infiltrate of foamy histiocytes, which may or may not contain ceroid pigment. Multinucleated giant cells are also common →.



Rokitansky-Aschoff Sinus
The granulomatous inflammation is often centered on a Rokitansky-Aschoff sinus, which may have previously ruptured. The one seen here is dilated and filled with bile. Note the foamy histiocytes, cholesterol clefts, and giant cells to the right.

TERMINOLOGY

Synonyms

- Cholegranulomas/cholecystic granulomas
- Ceroid granulomas

Definitions

- Variant of chronic cholecystitis featuring florid proliferation of foamy macrophages and granulomatous reaction to bile
  - Named due to histologic similarity to xanthogranulomatous pyelonephritis

ETIOLOGY/PATHOGENESIS

Reaction to Bile

- Usually preceded by rupture of Rokitansky-Aschoff sinus
  - Bile and lipid extruded into gallbladder wall, producing granulomatous reaction

CLINICAL ISSUES

Epidemiology

- Incidence
  - 4-9% of cholecystectomy specimens

Presentation

- Similar to chronic cholecystitis
- Majority of cases associated with gallstones

Treatment

- Cholecystectomy

Prognosis

- Surgery is generally curative
  - Rarely, inflammation extends from gallbladder to other organs to form adhesions or fistulas
  - Some reports of higher complication rates in xanthogranulomatous cholecystitis
- No established association with cholangiocarcinoma
  - Rare reports of elevated CA19-9 associated with xanthogranulomatous cholecystitis

IMAGING

Ultrasonographic Findings

- Thickened wall with echogenic, isoechoic, or hyperechoic nodules

MACROSCOPIC

General Features

- Tumor-like masses, nodules, or plaques
  - Often multiple
  - Usually intramural
    - Can produce mucosal masses as well, with overlying mucosal ulceration
  - Cream to brown color
  - Poorly circumscribed and soft
- Gallbladder wall often markedly thickened (up to 2 cm)

Size

- Range from few millimeters up to 3 cm

MICROSCOPIC

Histologic Features

- Spectrum of granulomatous lesions
  - Usually centered on ruptured Rokitansky-Aschoff sinuses
  - Granulomatous inflammation forms mural nodules
    - Mucosal surface may ulcerate as nodules expand
  - Foamy histiocyte infiltrate
    - Histiocytes may contain light brown ceroid granules, fat, or cholesterol crystals
    - Occasionally histiocytes are spindled
  - Well- or loosely formed granulomas
    - Bile may be present in center
    - Multinucleated giant cells common, often containing cholesterol clefts
  - Mixture of other inflammatory cells, especially lymphocytes, with occasional neutrophils
- Pools of extravasated bile may be present in wall of gallbladder
- Over time, organization occurs, and fibrosis may predominate
  - Calcifications also seen in older lesions

DIFFERENTIAL DIAGNOSIS

Carcinoma

- Nodules and markedly thickened wall of xanthogranulomatous cholecystitis can mimic malignancy both grossly and radiographically
  - Surgeons may submit frozen section of xanthogranulomatous cholecystitis to rule out malignancy
  - If spindled, macrophages can mimic mesenchymal neoplasm

– Macrophages mark with CD68, CD163

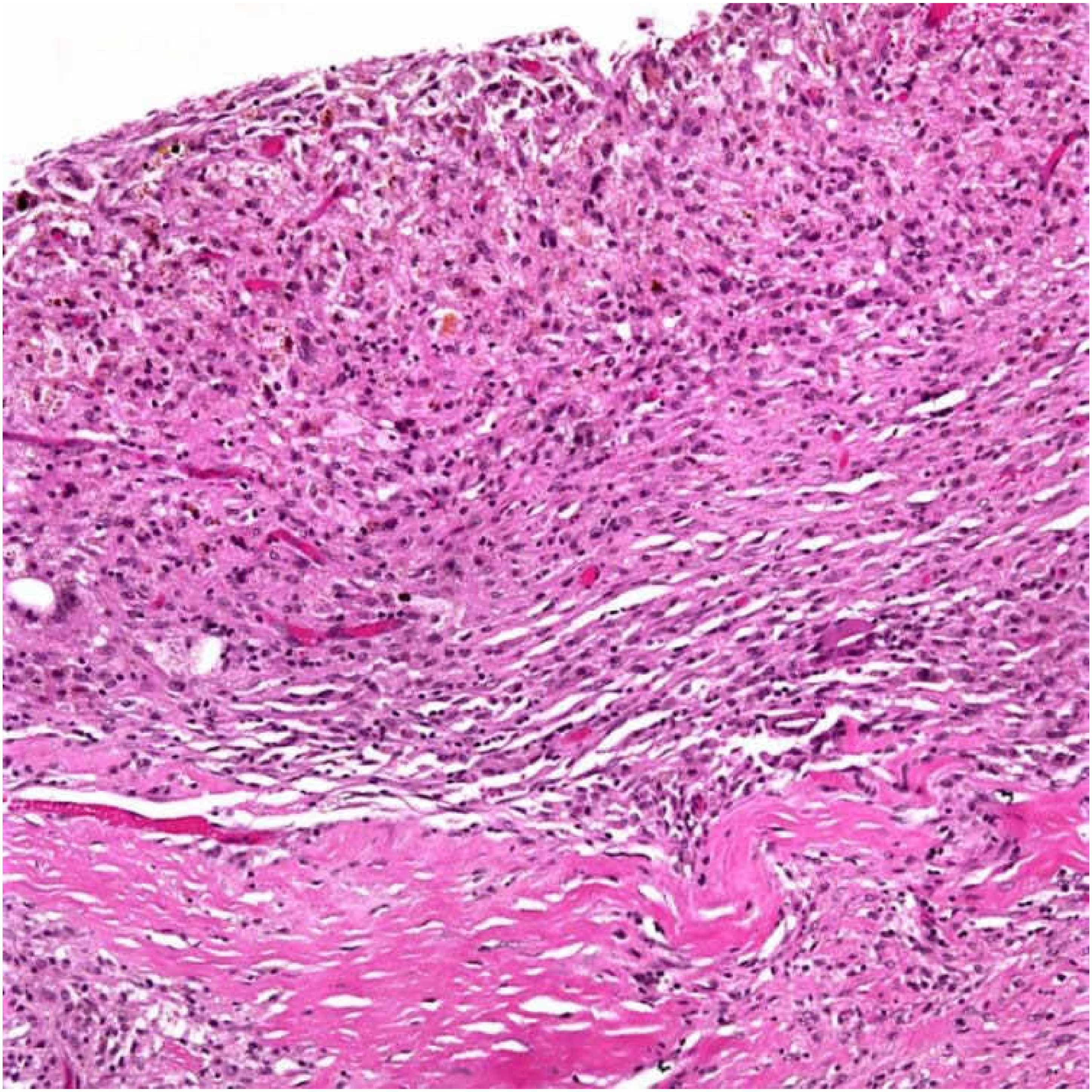
Malakoplakia

• Has Michaelis-Gutmann bodies
• Lacks ceroid-laden histiocytes, cholesterol clefts, and bile

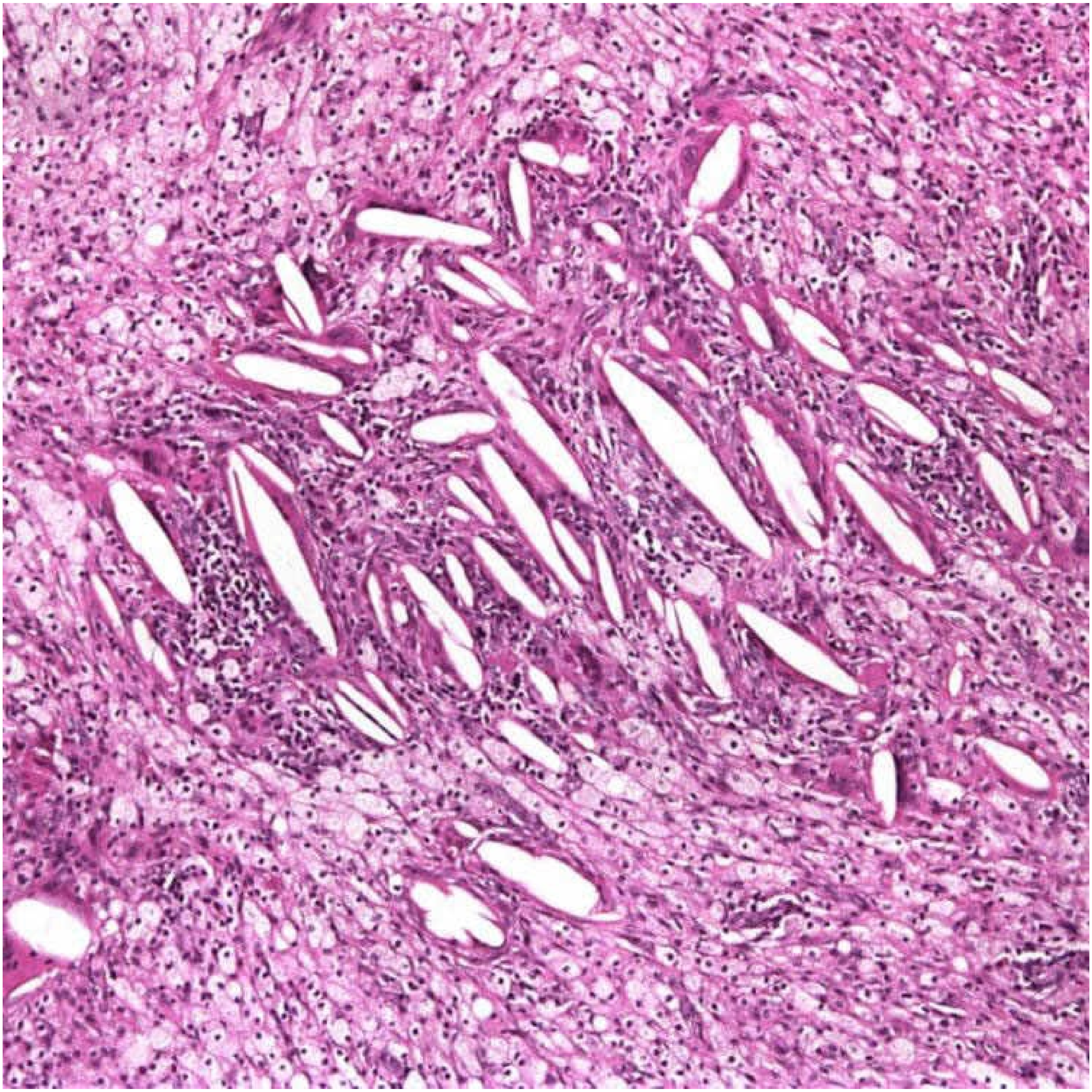
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

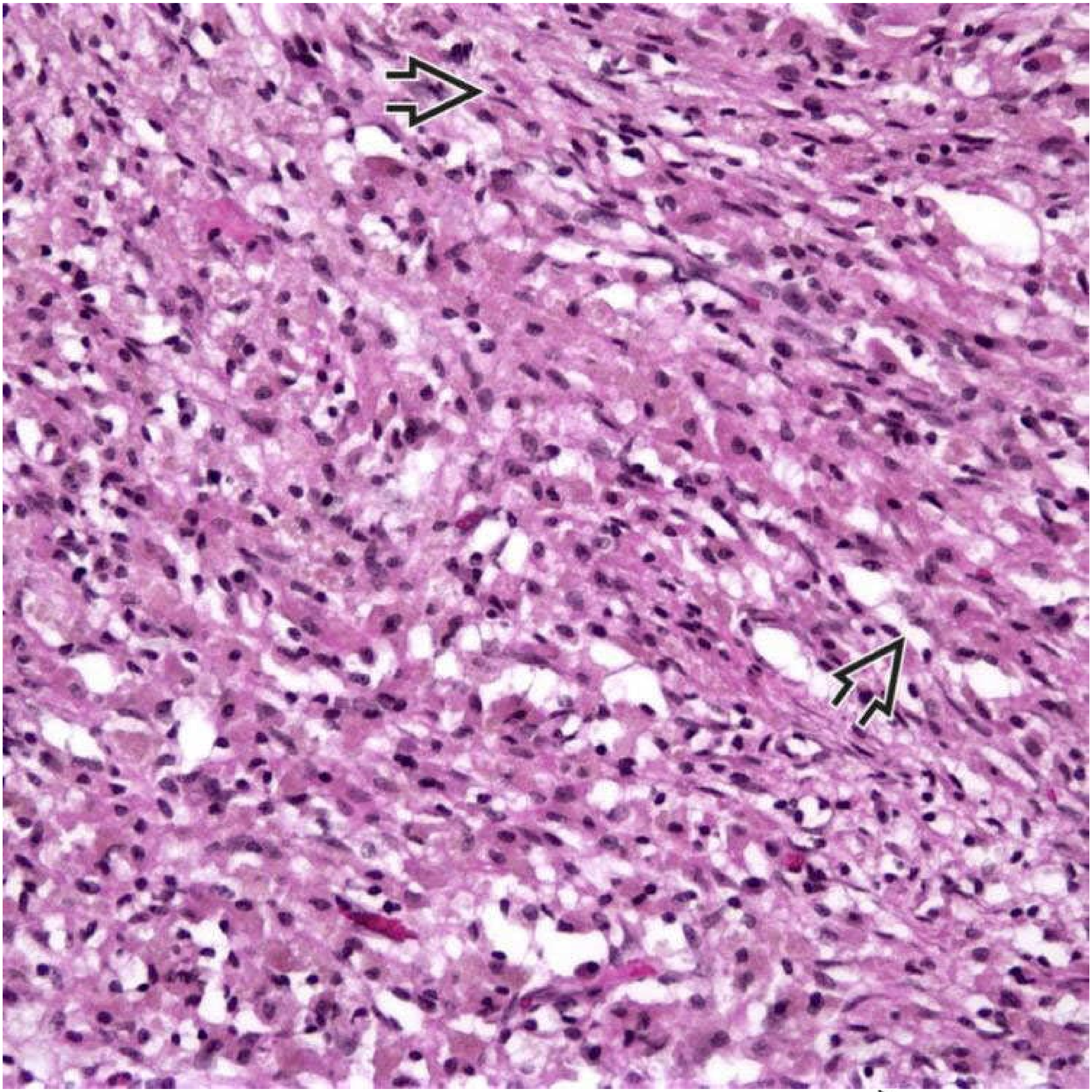
• Markedly thickened gallbladder wall may mimic malignancy grossly and radiographically



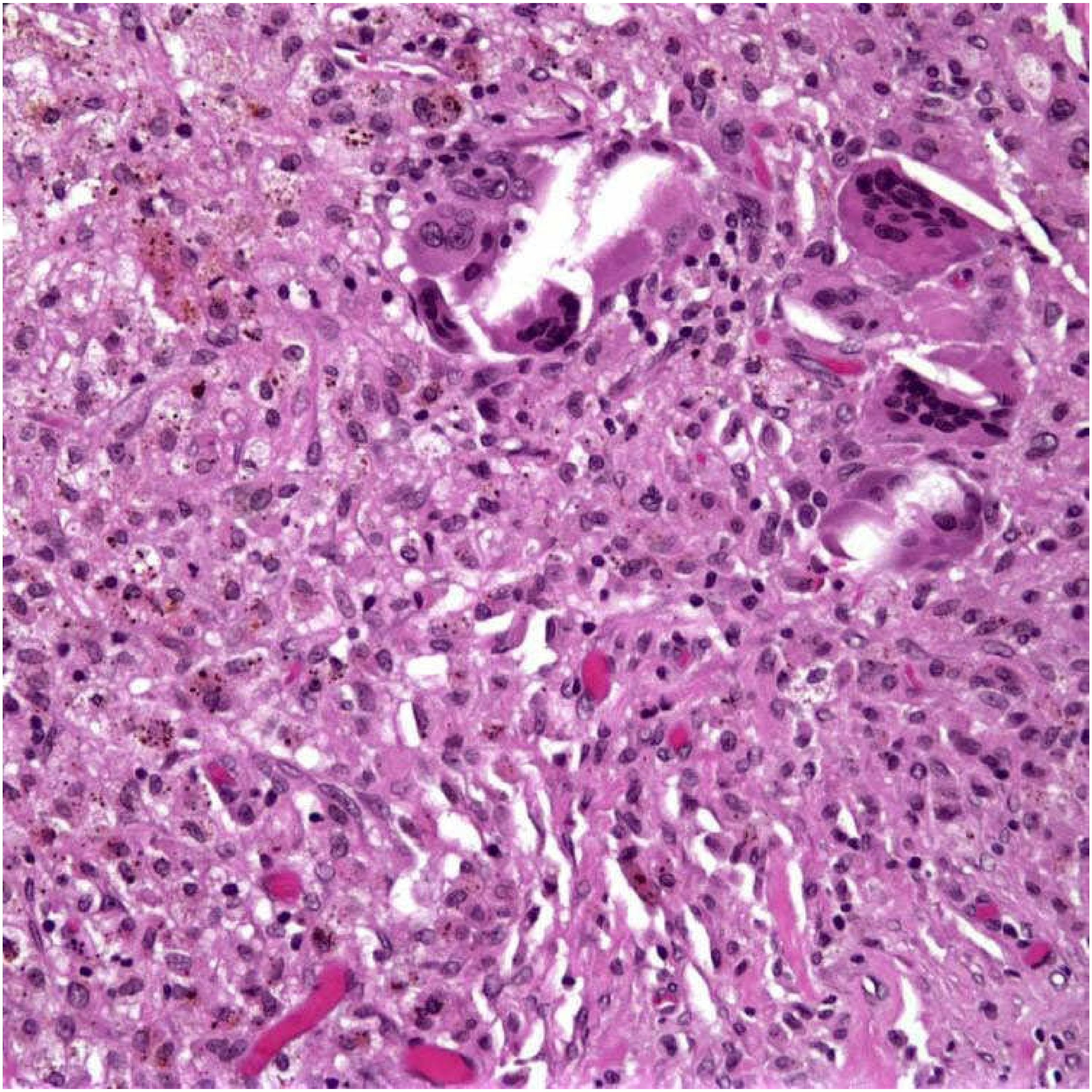
This section from the wall of the gallbladder shows a nodular infiltrate of histiocytes, many of which contain golden-brown ceroid pigment.

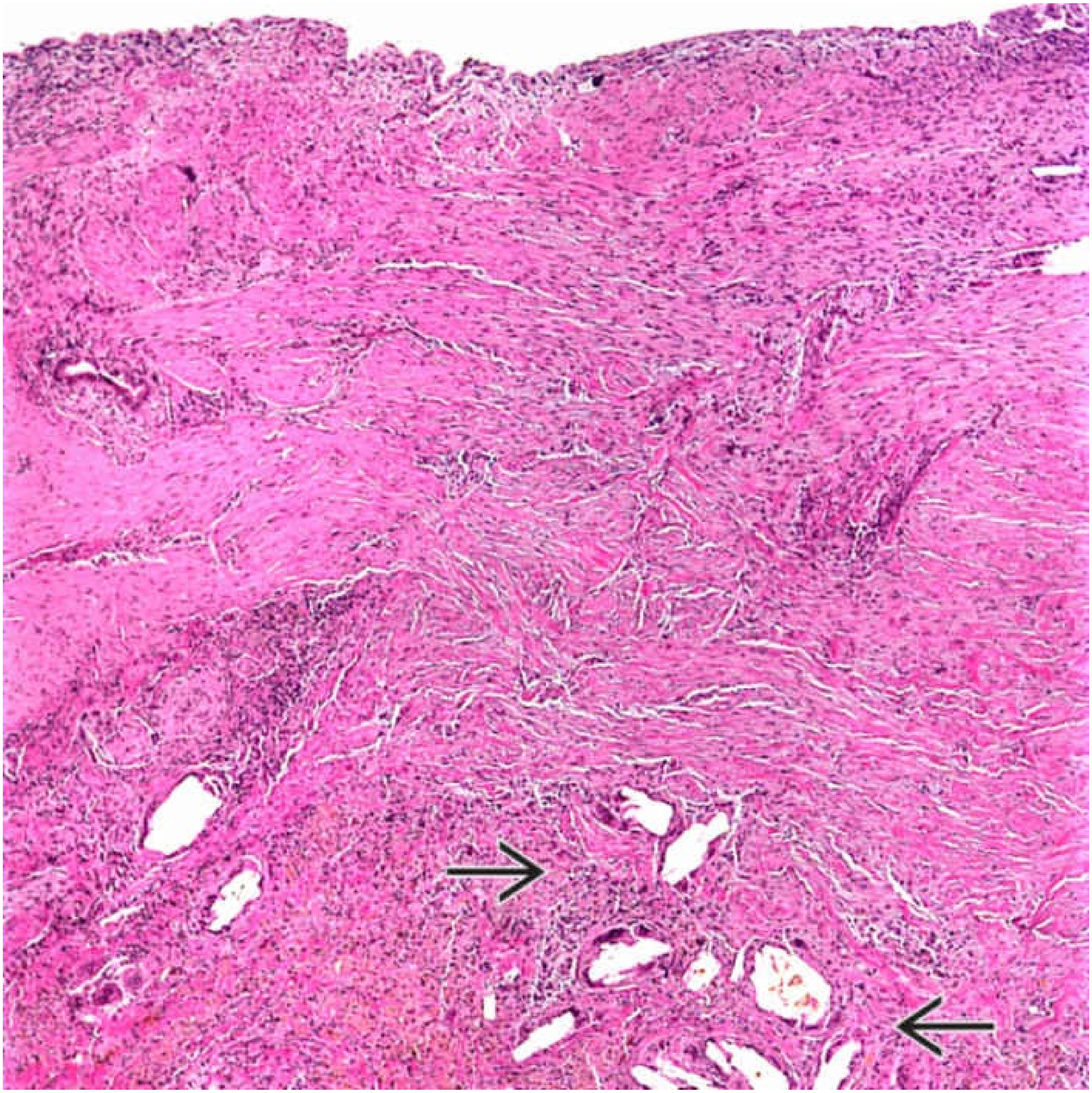


This cholegranuloma shows a foamy histiocyte infiltrate with numerous cholesterol clefts and scattered giant cells.

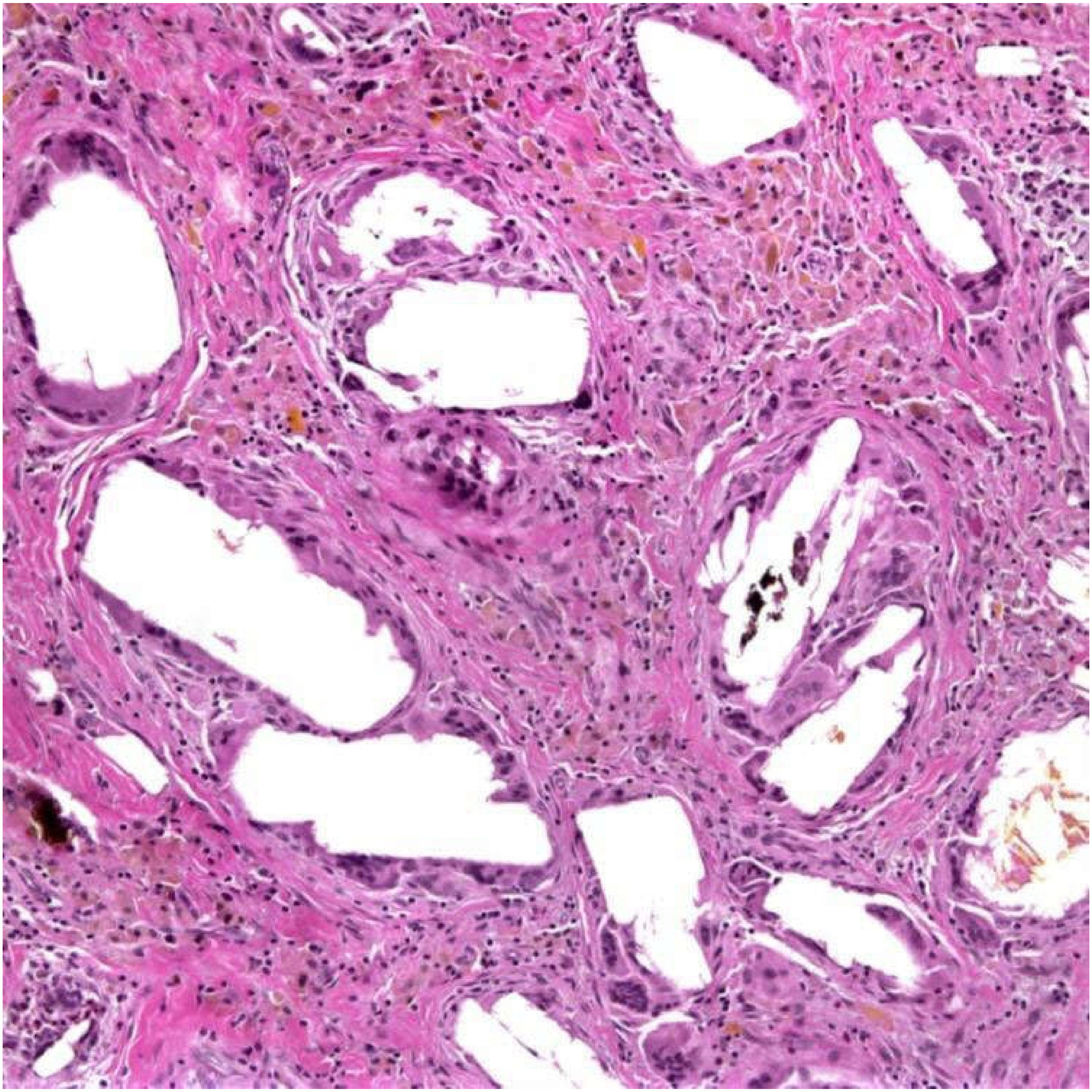


The histiocytes within xanthogranulomatous cholecystitis may be spindled .


Giant cells with cholesterol clefts are common. Note the surrounding infiltrate of macrophages, which contain ceroid pigment.



Xanthogranulomatous cholecystitis often features a markedly thickened wall with overlying mucosal ulceration. Note the associated cholesterol clefts → in the granulomatous inflammation.



This cholegranuloma shows a foamy histiocyte infiltrate with numerous cholesterol clefts, ceroid pigment, and scattered giant cells.

SELECTED REFERENCES

1. Deng, YL, et al. Xanthogranulomatous cholecystitis mimicking gallbladder carcinoma: an analysis of 42 cases. *World J Gastroenterol*. 2015; 21(44):12653–12659.
2. Revzin, MV, et al. The gallbladder: uncommon gallbladder conditions and unusual presentations of the common gallbladder pathological processes. *Abdom Imaging*. 2014; 40(2):385–399.
3. Houston, JP, et al. Xanthogranulomatous cholecystitis. *Br J Surg*. 1994; 81(7):1030–1032.
4. Roberts, KM, et al. Xanthogranulomatous cholecystitis: clinicopathological study of 13 cases. *J Clin Pathol*. 1987; 40(4):412–417.
5. Fligiel, S, et al. Xanthogranulomatous cholecystitis: case report and review of the literature. *Arch*

Pathol Lab Med. 1982; 106(6):302–304.
6.Goodman, ZD, et al. Xanthogranulomatous cholecystitis. *Am J Surg Pathol*. 1981; 5(7):653–659.

Eosinophilic Cholecystitis

KEY FACTS

Terminology

- Inflammatory disease of gallbladder in which inflammatory infiltrate is composed predominantly of eosinophils
    - Probably not distinct entity, but rather descriptive designation with associated clinical correlates

Etiology/Pathogenesis

- Majority of cases have no known cause or disease association
    - Some associated with hypersensitivity reactions, parasitic infection, other eosinophilic diseases
    - Hypersensitivity reaction to bile and bile stones has been hypothesized but never proven

Clinical Issues

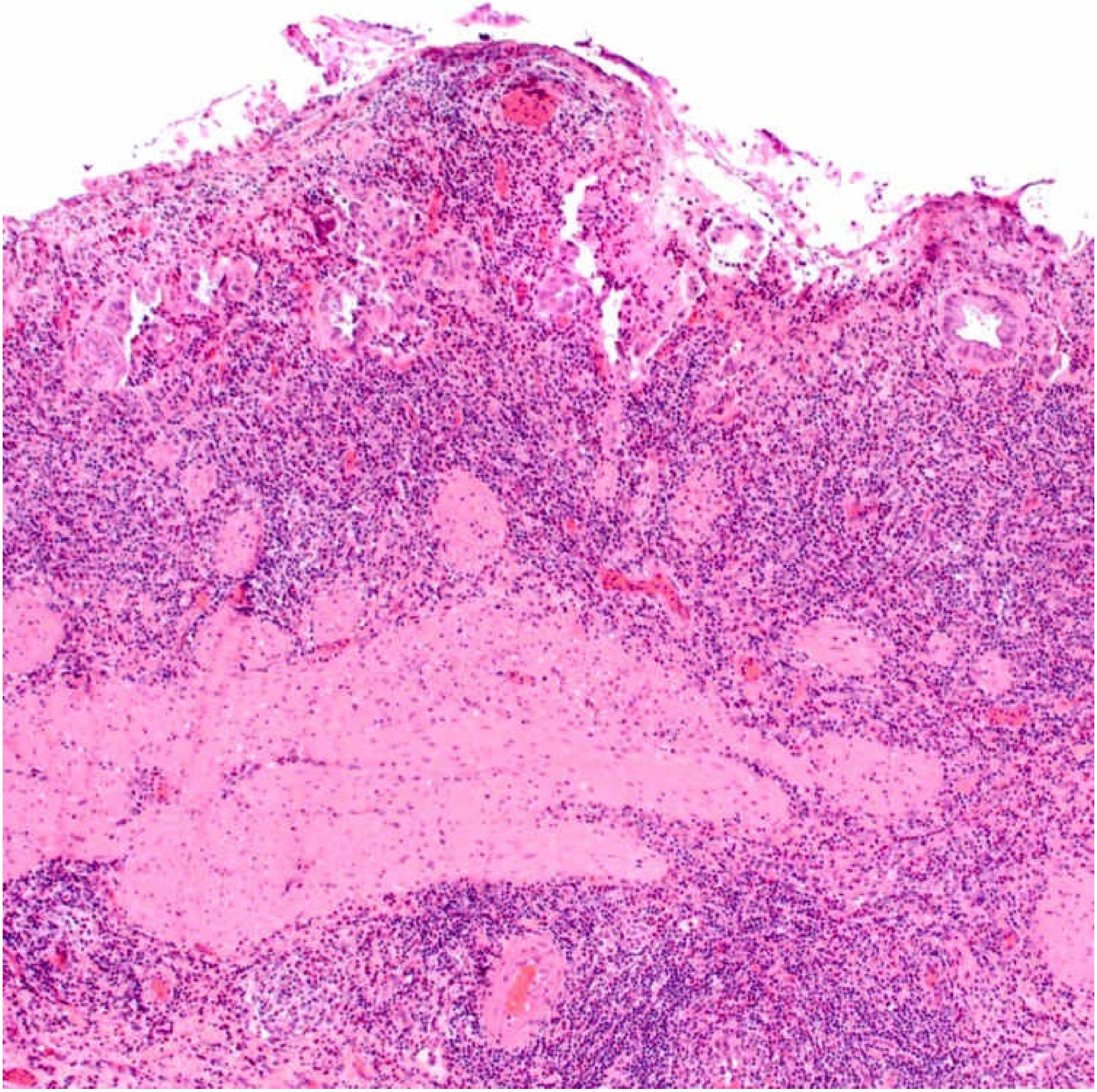
- Presenting signs are similar to other forms of cholecystitis
- Peripheral eosinophilia variably present
- Typically acalculous
- Diagnosis virtually always made following resection of gallbladder for symptomatic disease

Macroscopic

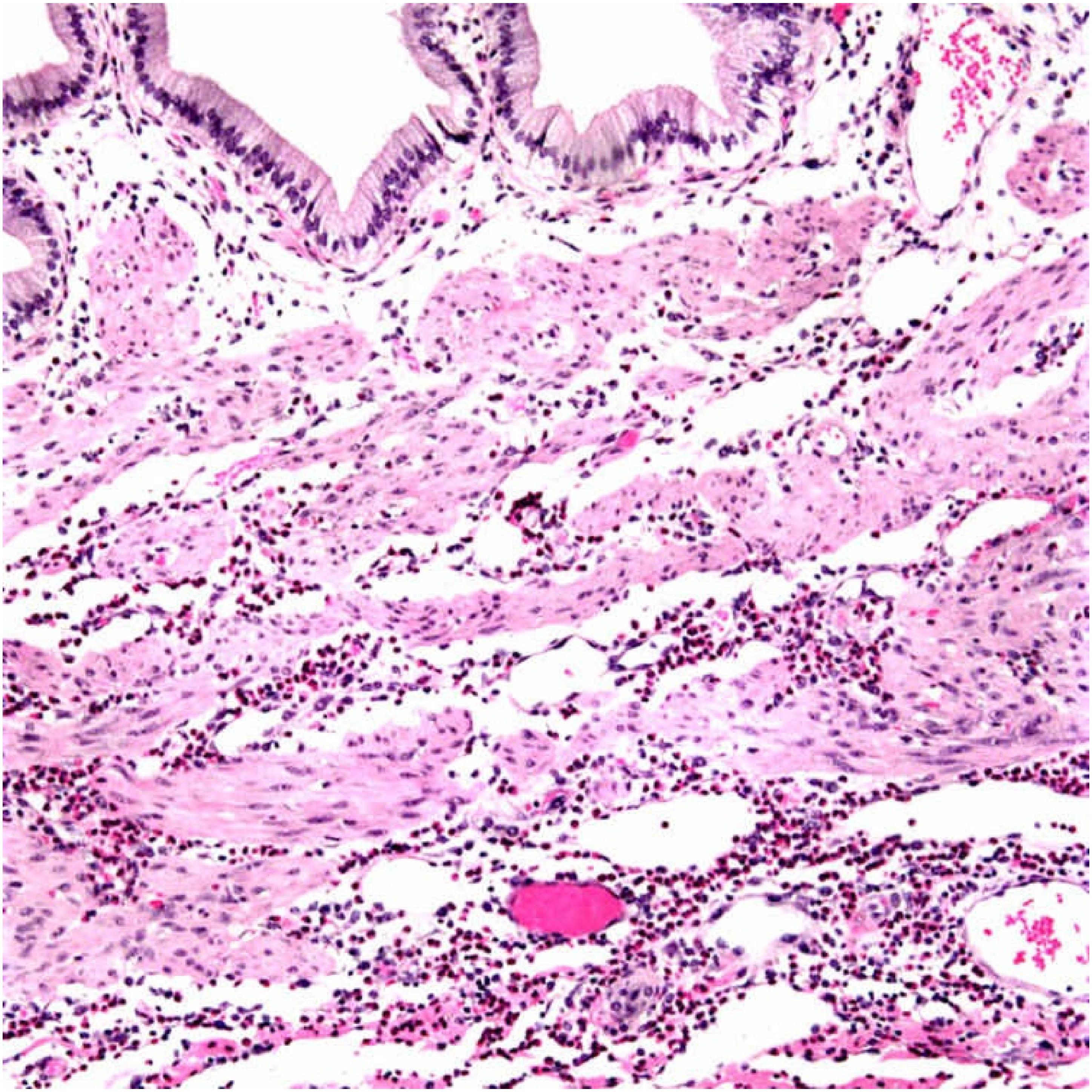
- Thickened gallbladder wall, usually without gallstones

Microscopic

- Dense eosinophilic infiltrate of gallbladder ± lymphocytic inflammatory component
    - Typically > 50% of inflammatory infiltrate is composed of eosinophils
    - So-called lymphoeosinophilic cholecystitis shows significant component of lymphocytes as well
    - In “true” or “pure” eosinophilic cholecystitis, close to 100% of inflammatory component is composed of eosinophils
- Specimen should be carefully evaluated for parasites

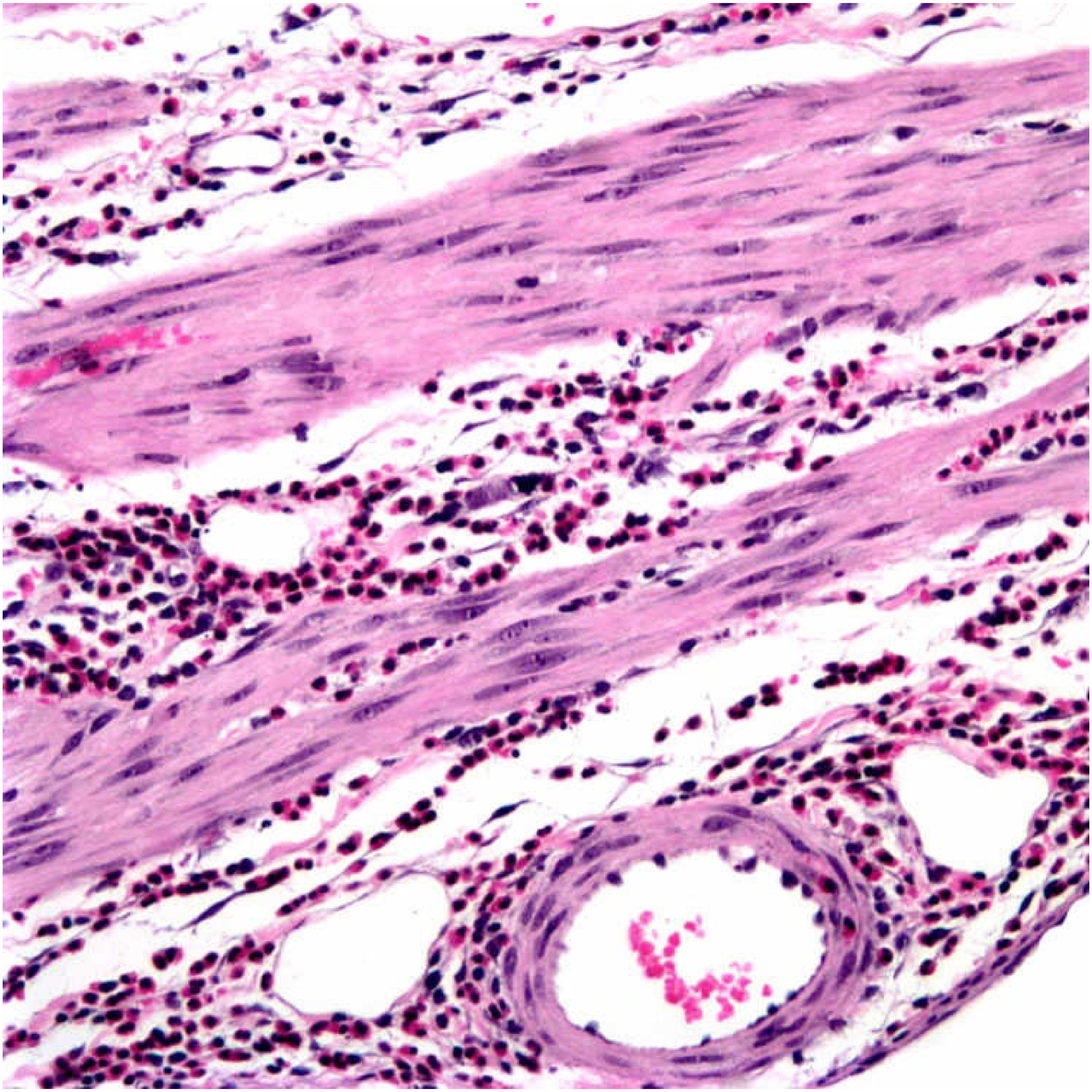


Transmural Eosinophilic Infiltrate
This case of eosinophilic cholecystitis shows a transmural infiltrate consisting of both lymphocytes and a prominent component of eosinophils.

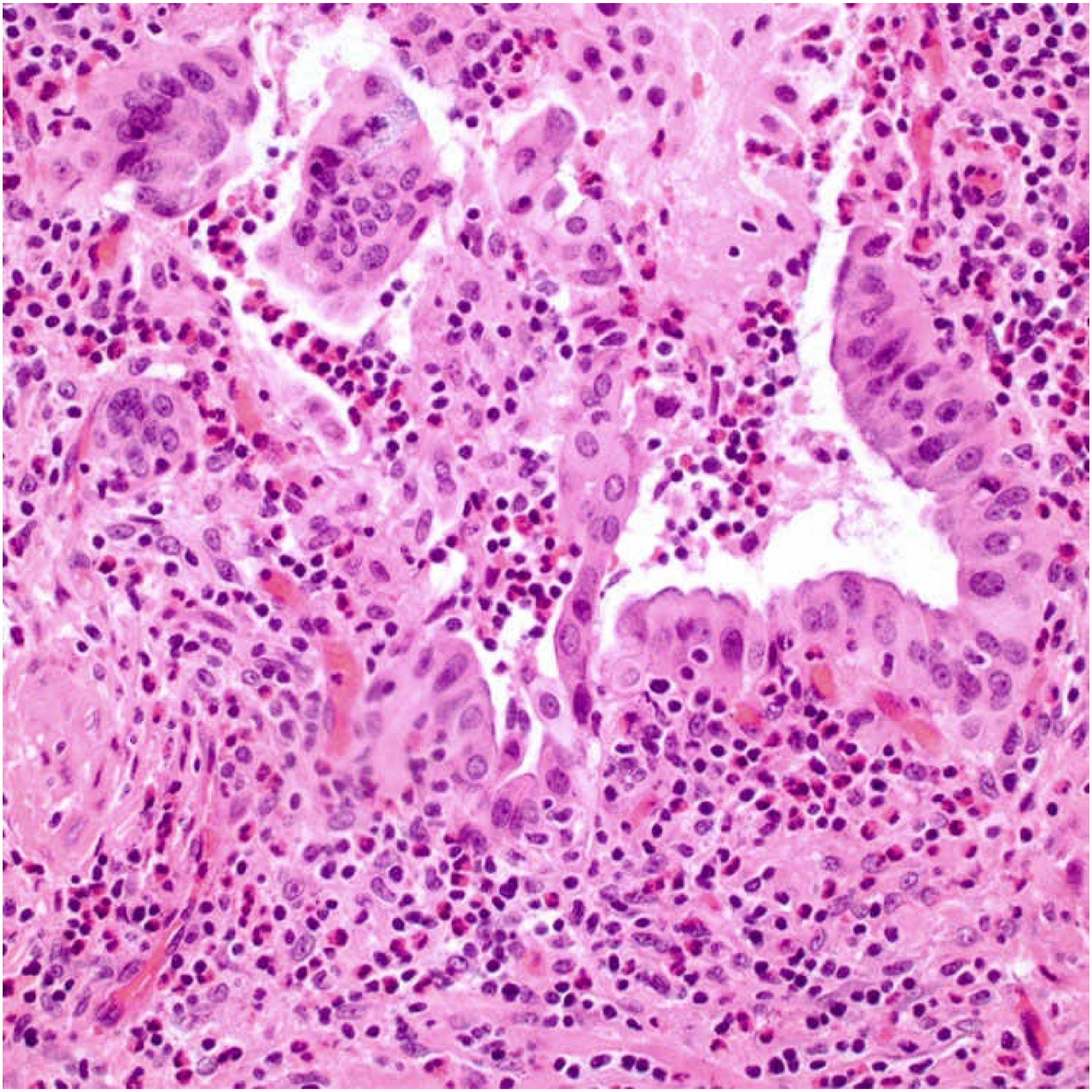


Pure Eosinophilic Infiltrate

This case of “pure” eosinophilic cholecystitis shows an exclusively eosinophilic infiltrate extending into the muscular wall of the gallbladder.



“Pure” Eosinophilic Infiltrate, High Power
This high-power view of “pure” eosinophilic cholecystitis shows the eosinophils within the wall of the gallbladder as well as surrounding vessels. However, unlike eosinophilic vasculitis, the vessels are not significantly infiltrated or damaged.



Mixed Lymphocytic/Eosinophilic Inflammation
Some cases of eosinophilic cholecystitis also have admixed lymphocytes in the inflammatory infiltrate, but typically > 50% of the infiltrate is composed of eosinophils.

TERMINOLOGY

Abbreviations

• Eosinophilic cholecystitis (EC)

Definitions

• Inflammatory disease of gallbladder in which inflammatory infiltrate is composed predominantly of

eosinophils

- Some advocate for reserving this term for cases in which infiltrate is purely eosinophilic
- Probably not distinct entity, but rather descriptive designation with some associated clinical correlates

ETIOLOGY/PATHOGENESIS

No Specific Cause in Most Cases

- Hypersensitivity reaction to bile and bile stones has been hypothesized but never proven
  - Some cases associated with hypersensitivity reaction to drugs, infections (*Echinococcus, Clonorchis sinensis*)
  - Some cases associated with other eosinophilic diseases
    - Eosinophilic gastroenteritis, eosinophilic cholangitis, hypereosinophilic syndrome
- Majority of cases have no specific underlying cause or disease association

CLINICAL ISSUES

Presentation

- Presenting signs are similar to other forms of acute and chronic cholecystitis
  - Right upper quadrant pain, biliary colic
- Peripheral eosinophilia
  - Frequently but not invariably present
- Typically acalculous cholecystitis
  - Although calculi are sometimes seen, stones are less commonly seen in EC than in other forms of acute and chronic cholecystitis

Treatment

- Cholecystectomy
  - Diagnosis is invariably made following evaluation of gallbladder specimen
- In rare instances when preoperative diagnosis has been made, steroid therapy is reported to be effective

Prognosis

- Cholecystectomy is curative, and disease does not recur

MACROSCOPIC

General Features

- Thickened gallbladder wall
- Gallstones are usually absent

MICROSCOPIC

Histologic Features

- Thickened and inflamed gallbladder wall
  - Predominantly eosinophilic infiltrate
  - – Typically > 50% of inflammatory infiltrate is composed of eosinophils
  - – Sheets and clusters of eosinophils infiltrate mucosa, muscularis propria, and subserosa
  - – Inflammation may preferentially involve one layer of gallbladder wall, or may be transmural
- Variations
  - In "true" or "pure" EC, close to 100% of inflammatory component is composed of eosinophils
    - – More rare than lymphoeosinophilic form
  - So-called lymphoeosinophilic cholecystitis shows significant component of lymphocytes as well

DIFFERENTIAL DIAGNOSIS

Chronic Cholecystitis

- Subacute phase of acute cholecystitis may show significant tissue eosinophilia
- Dense sheets and significant clustering of eosinophils are not seen in chronic calculous cholecystitis

Acute and Subacute Cholecystitis With Cholelithiasis

- Frequent admixture of neutrophils and eosinophils, particularly in instances of acute cholecystitis in which cholecystectomy is delayed
- Eosinophils do not typically dominate infiltrate, however

Autoimmune Pancreatitis-Associated Cholecystitis

- Gallbladder inflammation associated with autoimmune pancreatitis is dominated by lymphocytes and plasma cells
  - Can show significant numbers of eosinophils
- Elevated numbers of IgG4(+) plasma cells help distinguish this entity from EC

Churg-Strauss Syndrome

- EC lacks significant vascular infiltration by eosinophils, and should not have vascular damage

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Predominance of eosinophils in inflamed gallbladder
  - Variably present gallstones
  - May be associated with other eosinophilic diseases or peripheral eosinophilia
  - Most cases have no specific disease association

SELECTED REFERENCES

1. Lai, CH, et al. Clonorchiasis-associated perforated eosinophilic cholecystitis. *Am J Trop Med Hyg*. 2007; 76(2):396–398.
2. Shakov, R, et al. Eosinophilic cholecystitis, with a review of the literature. *Ann Clin Lab Sci*. 2007; 37(2):182–185.
3. Suzuki, M, et al. Churg-Strauss syndrome complicated by colon erosion, acalculous cholecystitis and liver abscesses. *World J Gastroenterol*. 2005; 11(33):5248–5250.
4. Jimenez-Saenz, M, et al. Biliary tract disease: a rare manifestation of eosinophilic gastroenteritis. *Dig Dis Sci*. 2003; 48(3):624–627.
5. Dabbs, DJ. Eosinophilic and lymphoeosinophilic cholecystitis. *Am J Surg Pathol*. 1993; 17(5):497–501.
6. Parry, SW, et al. Acalculous hypersensitivity cholecystitis: hypothesis of a new clinicopathologic entity. *Surgery*. 1988; 104(5):911–916.
7. Kerstein, MD, et al. Eosinophilic cholecystitis. *Am J Gastroenterol*. 1976; 66(4):349–352.

Polyarteritis Nodosa and Other Vasculitides

KEY FACTS

Terminology

- Involvement of liver &/or gallbladder by vasculitis (inflammation of blood vessels)

Etiology/Pathogenesis

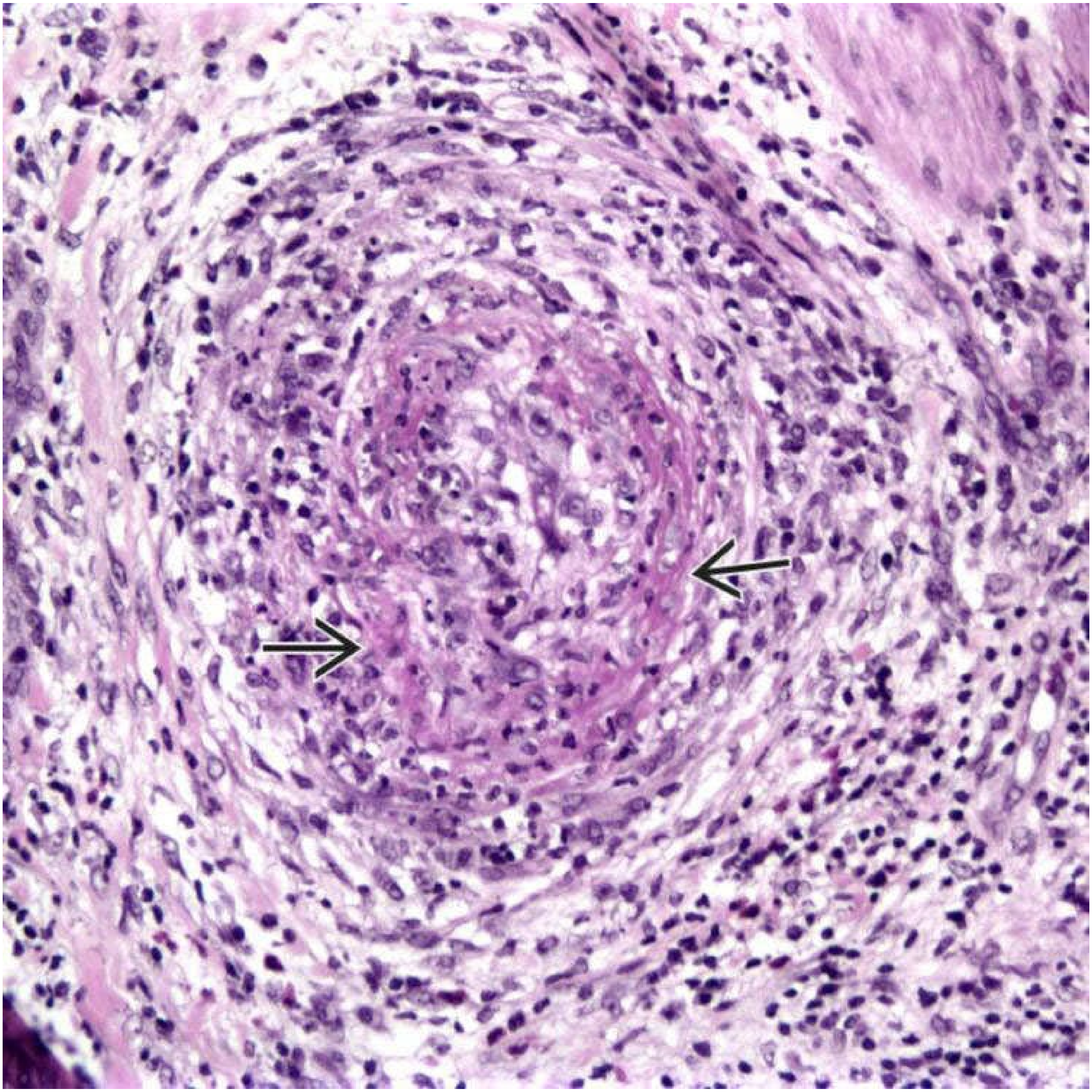
- Liver involved in > 40% of cases of polyarteritis nodosa (PAN)
  - Gallbladder involvement most often part of systemic disease
  - Occasionally isolated finding at cholecystectomy
  - Isolated form rarely progresses to systemic form, but systemic form may develop up to 1 year later
- Liver and gallbladder rarely involved in vasculitides other than PAN
  - Churg-Strauss syndrome
  - Rheumatoid arthritis
  - Henoch-Schönlein purpura
  - Lupus

Clinical Issues

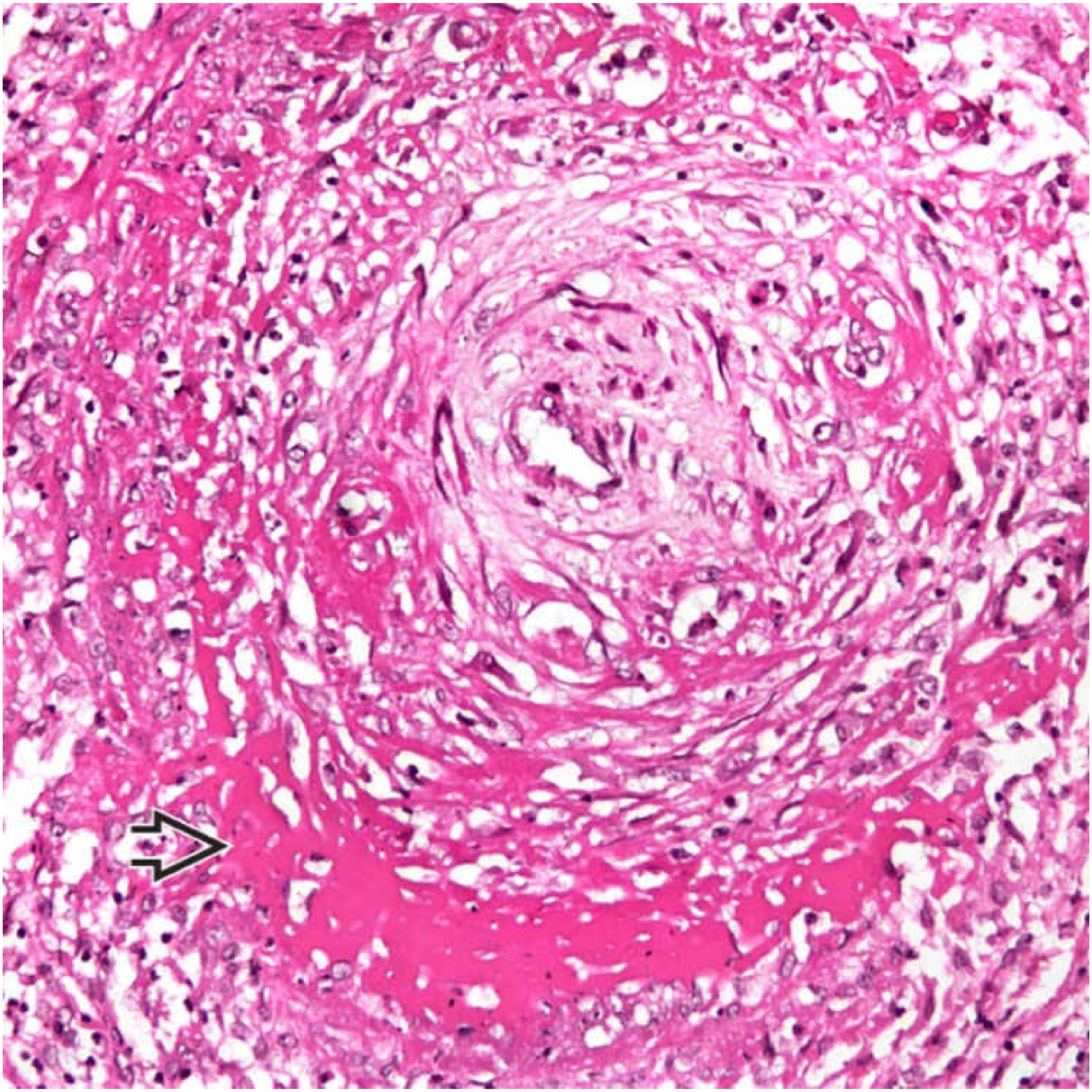
- Common presenting complaints include fever, abdominal pain
  - Signs/symptoms can mimic acute acalculous cholecystitis
- Laboratory findings usually reflect severe systemic inflammation
  - Elevated ESR, CRP, WBC count
- Treatment includes combination of steroids and immunosuppressive agents

Microscopic

- Hallmark lesion of PAN is fibrinoid necrosis and destructive inflammation involving medium-sized arteries
  - Initially involves media, with destruction of elastic laminae and smooth muscle
  - Only segment of wall may be affected
  - As healing occurs, bead-like nodular aneurysm (nodose) may form
  - – Admixture of early and late lesions is common

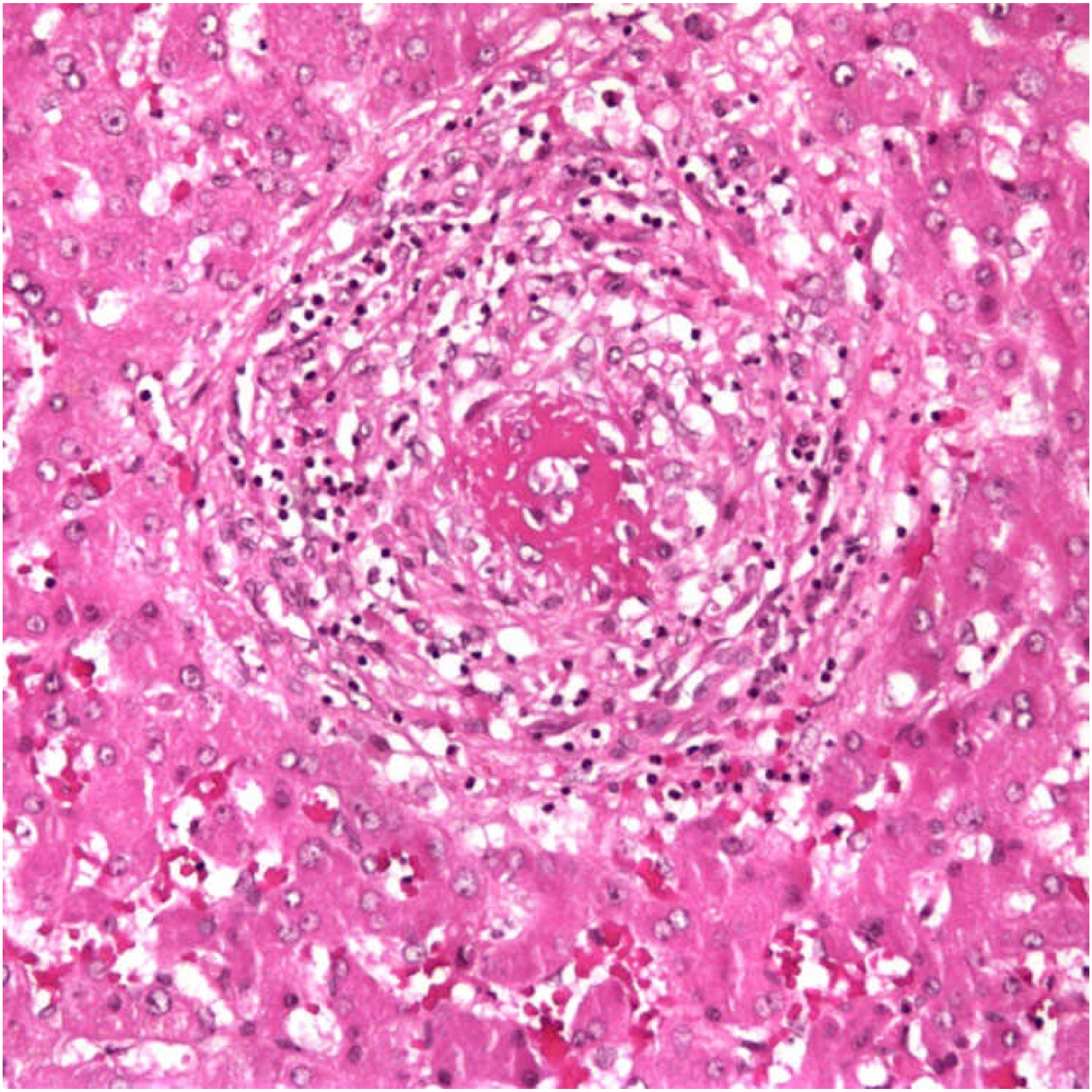


Fibrinoid Necrosis and Inflammation of Vessel Wall
This lesion from the gallbladder shows fibrinoid necrosis → and destructive inflammation of the vessel wall. The lumen is almost obliterated.

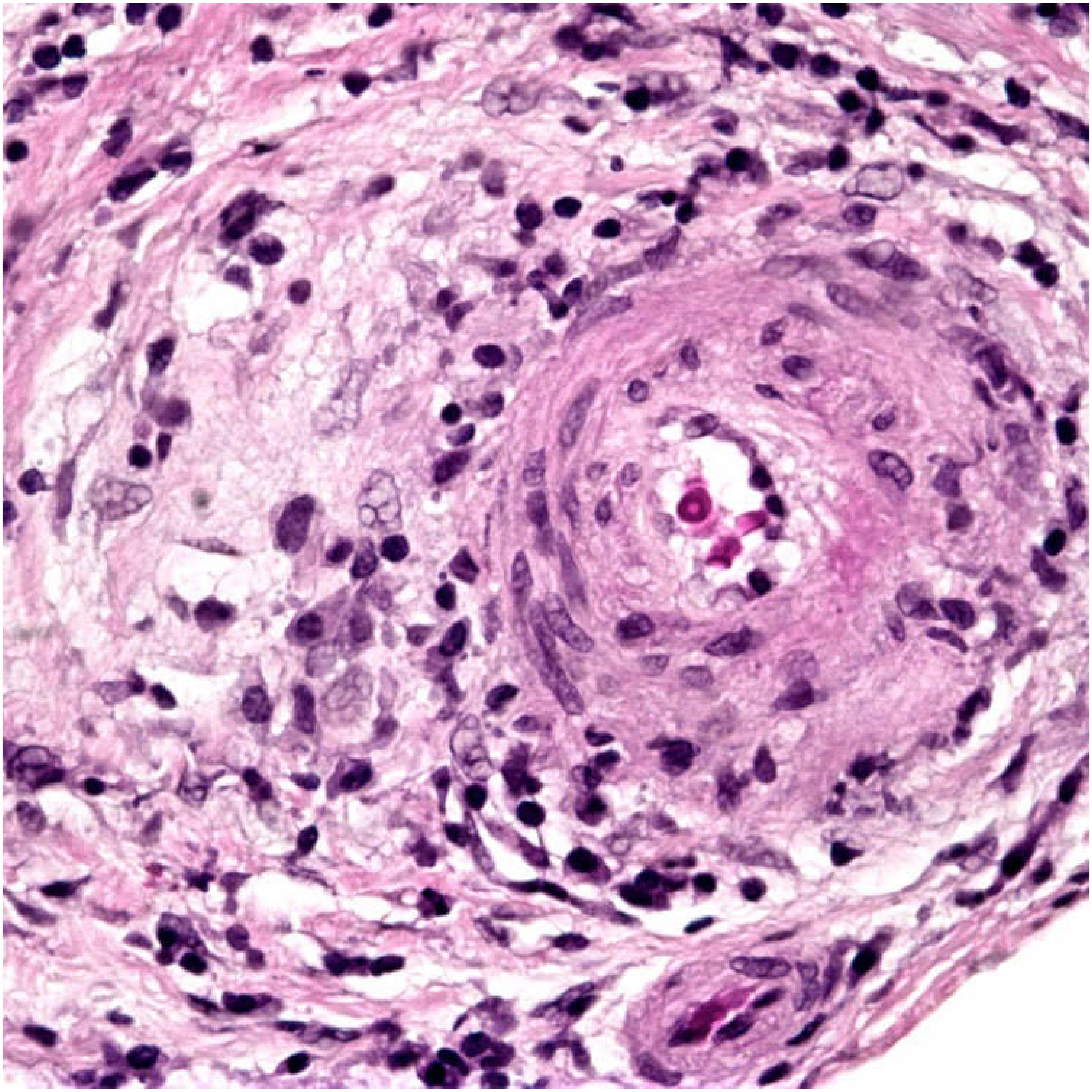


Fibrinoid Necrosis

Fibrinoid necrosis is seen within the wall of a medium-sized artery in the liver. This lesion is the hallmark of polyarteritis nodosa. Note the marked luminal compromise.



Inflammatory Destruction of Vessel Wall
A medium-sized artery in the liver shows fibrinoid necrosis and inflammatory destruction of the vessel wall.


Vessel With Scarring
Older lesions in polyarteritis nodosa show resolution of the necrosis and scarring of the vessel wall, sometimes with luminal compromise.

TERMINOLOGY

Abbreviations

- Polyarteritis nodosa (PAN)

Definitions

- Involvement of liver &/or gallbladder by vasculitis (inflammation of blood vessels)

ETIOLOGY/PATHOGENESIS

Liver

- Involved in > 40% of cases
  - Frequently associated with hepatitis B

Gallbladder

- Involved in 2 distinct settings
  - Isolated involvement (monoarterial or localized form)
    - Isolated form rarely progresses to systemic form, but systemic form may develop up to 1 year after isolated lesions found in cholecystectomy
    - Some patients have other systemic autoimmune diseases such as lupus or scleroderma
  - Part of systemic disease
    - Most common presentation
    - Gallbladder involved in up to 40% of cases of systemic disease

CLINICAL ISSUES

Presentation

- Signs and symptoms similar to acute acalculous cholecystitis
  - Systemic complaints: Fever, malaise/weakness, musculoskeletal pain, renal failure
  - Liver/gallbladder involvement may be clinically silent
  - Lesions discovered incidentally in tissue sections
- Sequelae
  - Hepatic infarction
  - Arterial rupture with intraabdominal hemorrhage
  - Nodular regenerative hyperplasia
  - Injury to intrahepatic bile ducts
- Liver and gallbladder rarely involved in vasculitides other than PAN
  - Churg-Strauss syndrome
    - Accompanied by asthma, pulmonary infiltrates, eosinophilia
    - Vasculitis is granulomatous
  - Rheumatoid vasculitis
    - Usually accompanied by severe arthritis, low complement, high levels of circulating antibodies
    - Necrotizing vasculitis resembling PAN
  - Systemic lupus erythematosus
    - Liver and gallbladder affected in persons with severe systemic disease
  - Henoch-Schönlein purpura
    - Accompanied by purpura, arthritis
    - Usually pediatric patients
  - Wegener granulomatosis
  - Temporal arteritis

- Takayasu arteritis
- Drug-induced vasculitis

Laboratory Tests

- Laboratory findings usually reflect severe systemic inflammation
    - Elevated ESR, C-reactive protein, WBC count, serum immunoglobulins
- Anemia may be present, secondary to blood loss or renal failure

Treatment

- Combination of steroids and immunosuppressive agents
    - Ongoing therapy may be required to maintain remission

IMAGING

Angiography

- May reveal aneurysms, evidence of vasculitis

MACROSCOPIC

Liver

- Gross evidence of infarction
- May be normal

Gallbladder

- Thickened, edematous wall

MICROSCOPIC

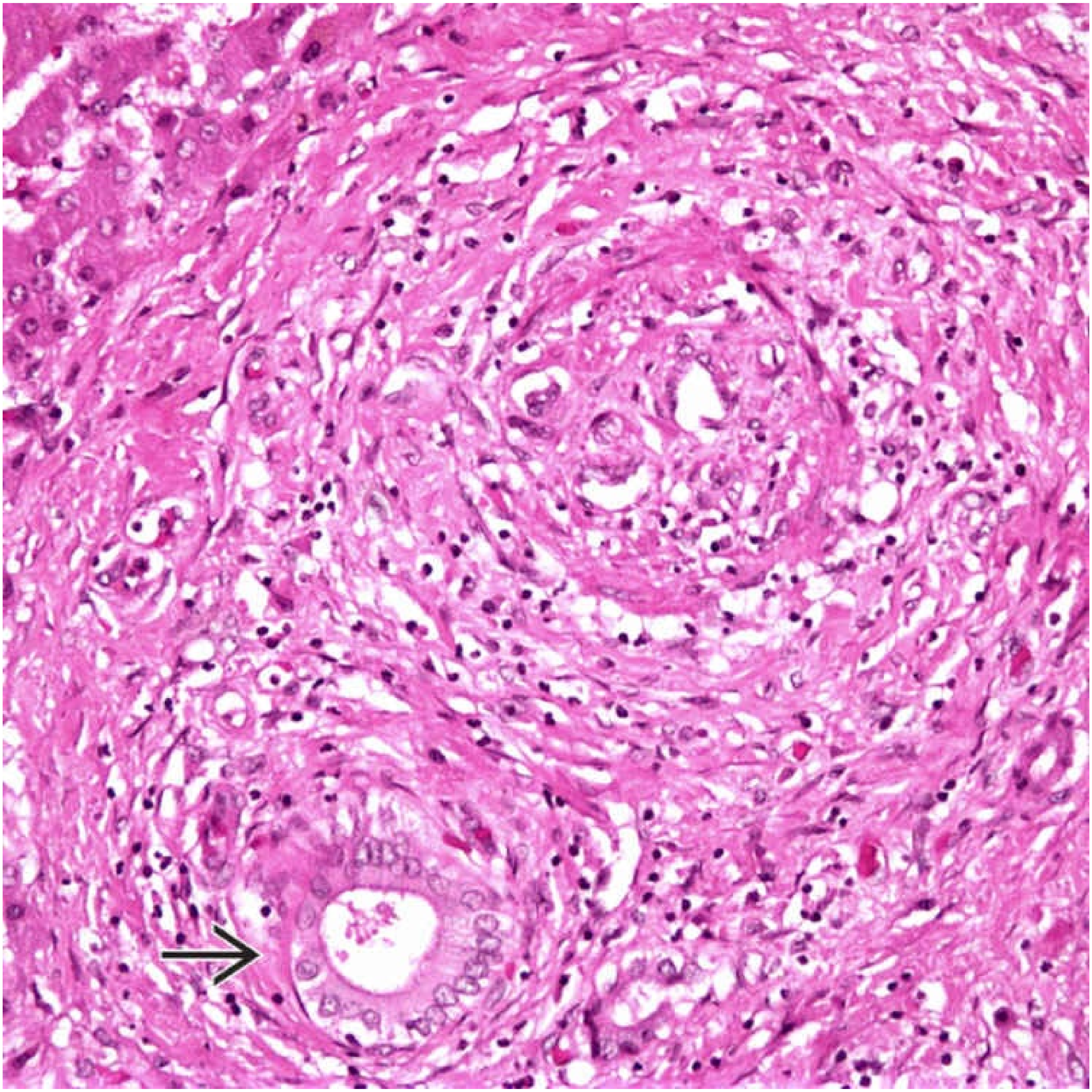
Histologic Features

- Hallmark lesion of PAN is fibrinoid necrosis involving medium-sized arteries
    - Initially involves media, with destruction of elastic laminae and smooth muscle
    - Only segment of wall may be affected
    - In acute phase, endothelial damage may cause thrombosis
    - As healing occurs, bead-like nodular aneurysm (nodose) may form
    - Recanalized thrombi may be seen
    - Usually, temporal mixture of lesions is present, ranging from early to completely scarred
- Often accompanied by mixed inflammatory infiltrate
    - Eosinophils may be prominent
- Infarction, mucosal ulceration (gallbladder) may be present

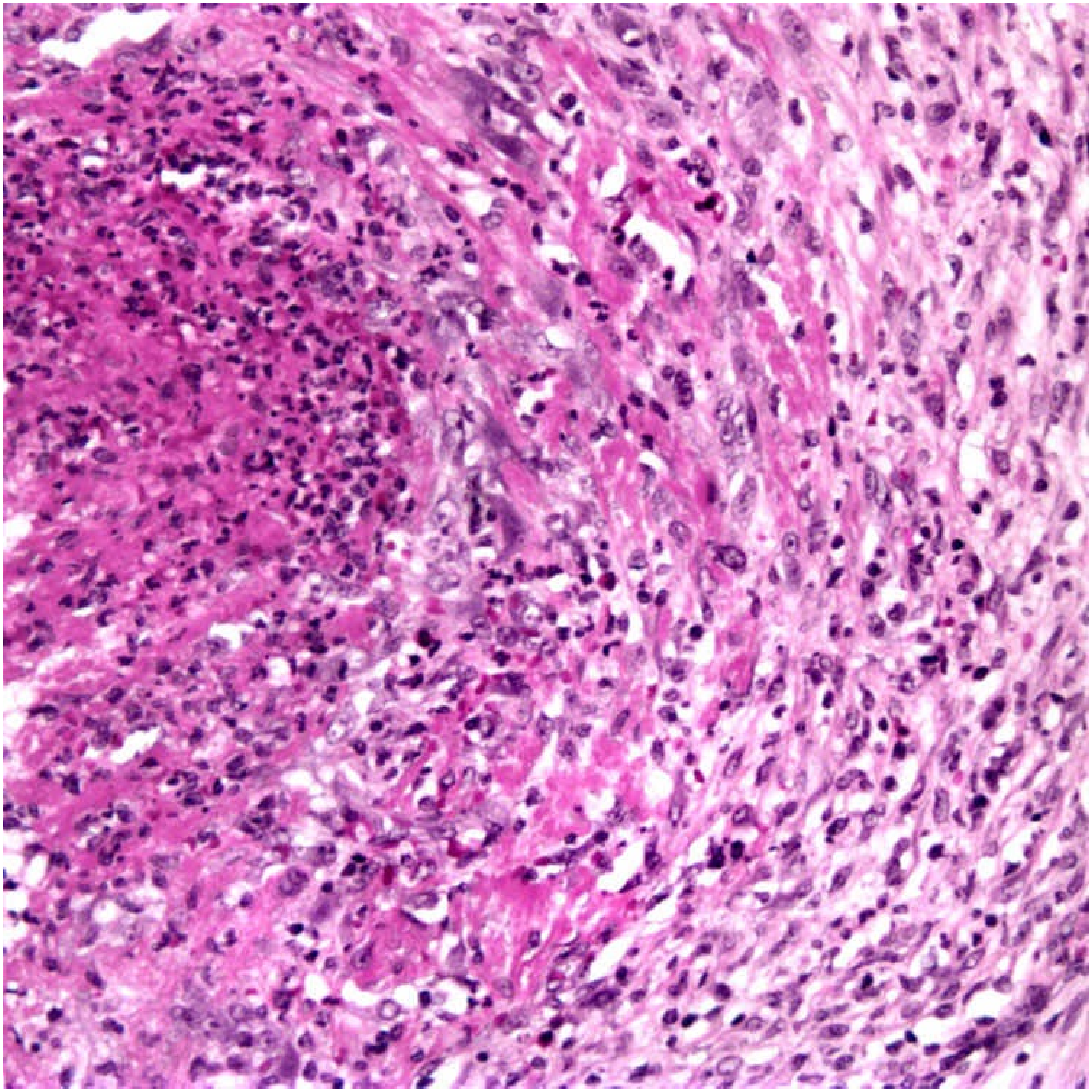
DIFFERENTIAL DIAGNOSIS

Cholecystitis

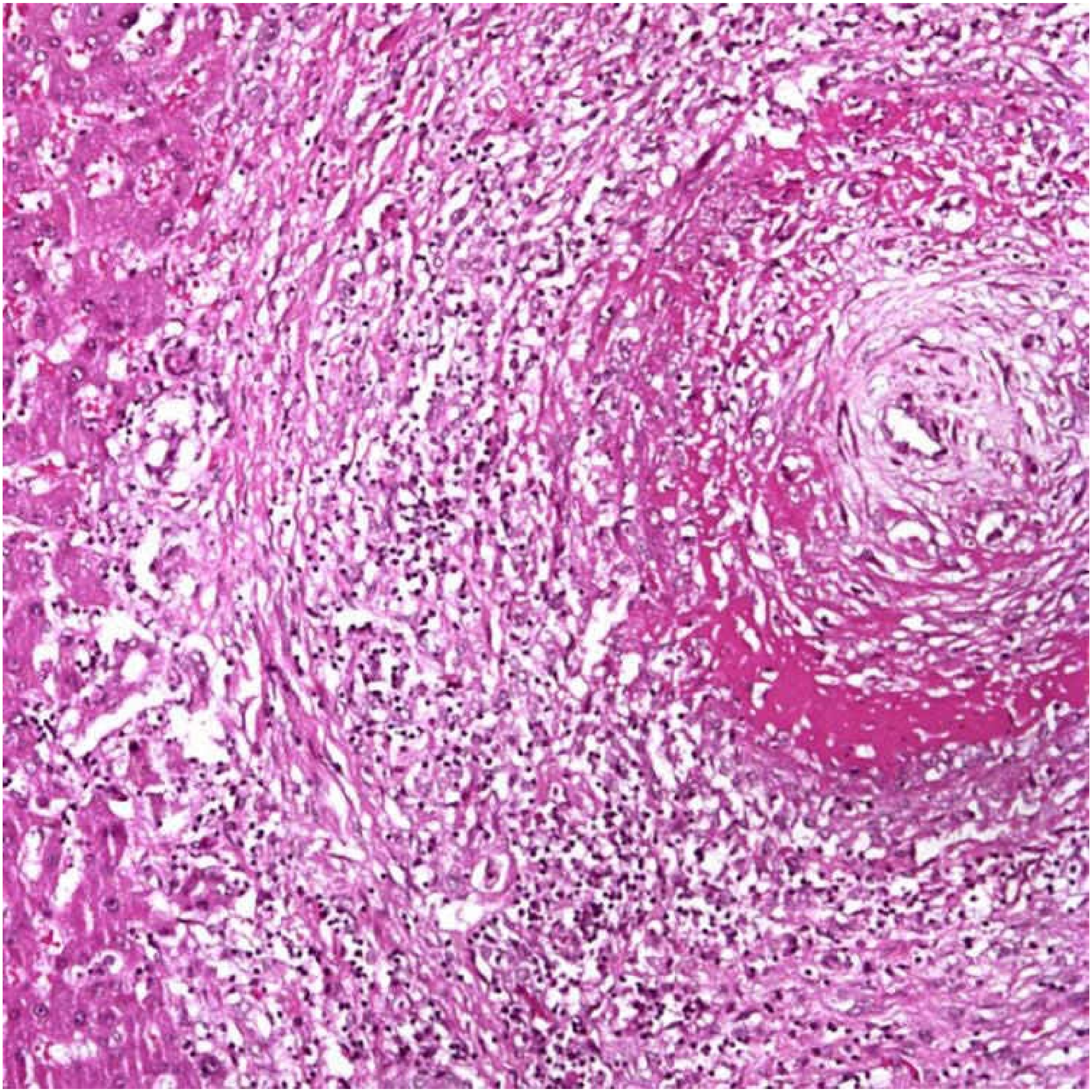
- Acute, chronic, and eosinophilic cholecystitis may show perivascular inflammation
    - Lack fibrinoid necrosis



This liver involved by polyarteritis nodosa features a medium-sized artery with fibrinoid necrosis, early fibrosis, and luminal narrowing. Note adjacent bile duct →.



This case of polyarteritis nodosa in the gallbladder shows fibrinoid necrosis and destruction of the artery wall with an associated mixed inflammatory infiltrate.



This vessel shows fibrinoid necrosis of the vessel wall, along with marked inflammation. The lumen is severely narrowed. Note the hepatic parenchyma to the right.

SELECTED REFERENCES

1. Hernández-Rodríguez, J, et al. Single-organ gallbladder vasculitis: characterization and distinction from systemic vasculitis involving the gallbladder. An analysis of 61 patients. *Medicine (Baltimore)*. 2014; 93(24):405–413.
3. De-Leon-Bojorge, B, et al. Thrombotic microangiopathy involving the gallbladder as an unusual manifestation of systemic lupus erythematosus and antiphospholipid syndrome: Case report and review of the literature. *World J Gastroenterol*. 2006; 12(44):7206–7209.
4. Bailey, M, et al. The effects of vasculitis on the gastrointestinal tract and liver. *Gastroenterol Clin North Am*. 1998; 27(4):747–782. [v-vi].

5. Burke, AP, et al. Localized vasculitis of the gastrointestinal tract. *Am J Surg Pathol*. 1995; 19(3):338–349.

2. Juliano, J, et al. Vasculitis of the gallbladder: case report and spectrum of disease. *J Clin Rheumatol*. 2009; 15(2):75–77.
6. Nøhr, M, et al. Isolated necrotizing panarteritis of the gallbladder. Case report. *Acta Chir Scand*. 1989; 155(9):485–487.

Parasitic Infection

KEY FACTS

Terminology

- Infection of bile ducts by parasite
  - Usually protozoan (*Microsporidia*, *Cryptosporidia*) or helminth (liver fluke, schistosomiasis, ascariasis)

Etiology/Pathogenesis

- *Cryptosporidium* species
- Trematodes
- Nematodes

Clinical Issues

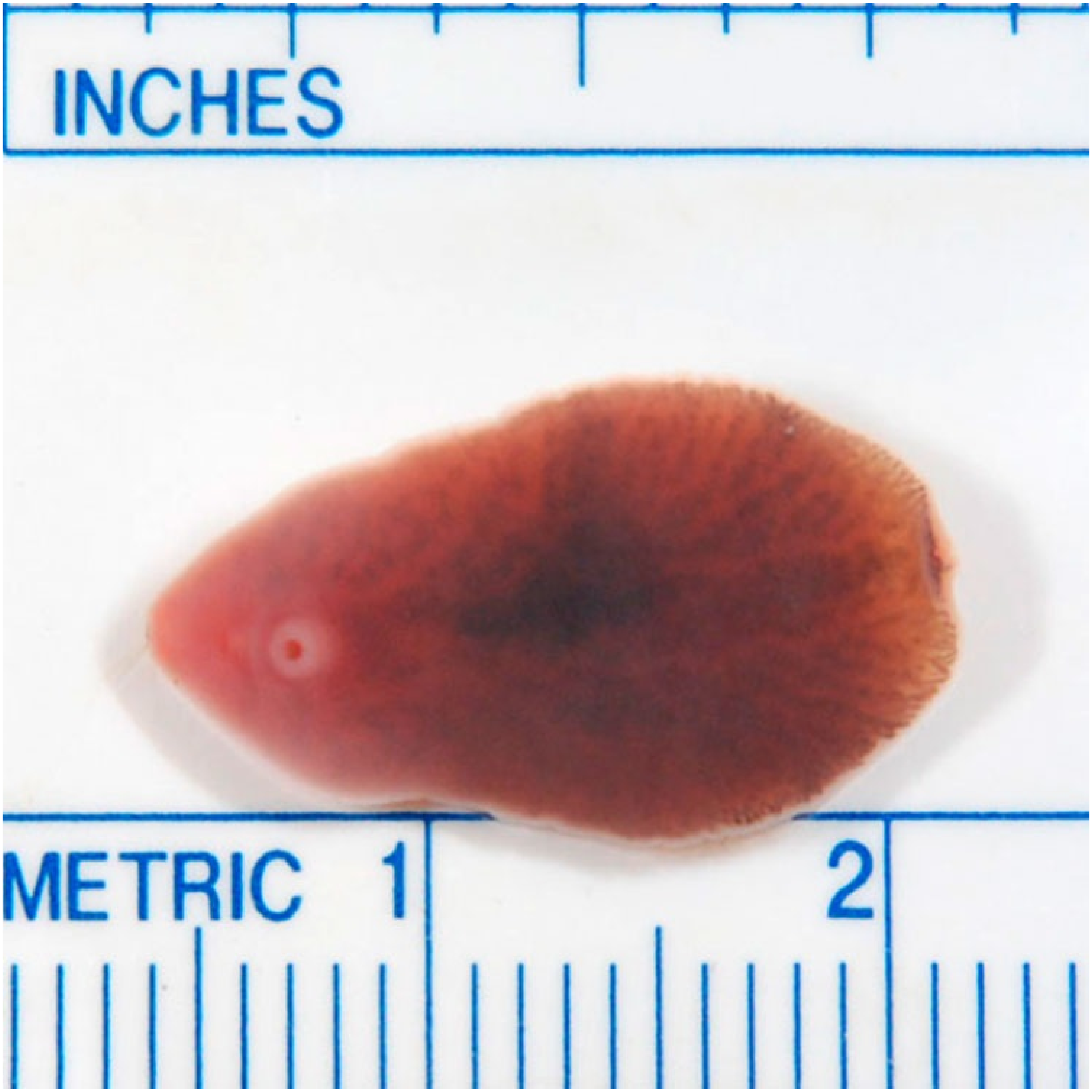
- Protozoal infection usually seen in context of AIDS (AIDS cholangiopathy)
  - Can mimic primary sclerosing cholangitis radiographically
- Helminths present with fever, right upper quadrant pain, signs of biliary obstruction
- Gradual and regular stenosis of common bile duct with dilation of intrahepatic bile ducts
- Prognosis depends on specific infection and status of host
  - Sequelae of *Clonorchis*, *Opisthorchis* infection include cholangiocarcinoma, Oriental cholangiohepatitis

Macroscopic

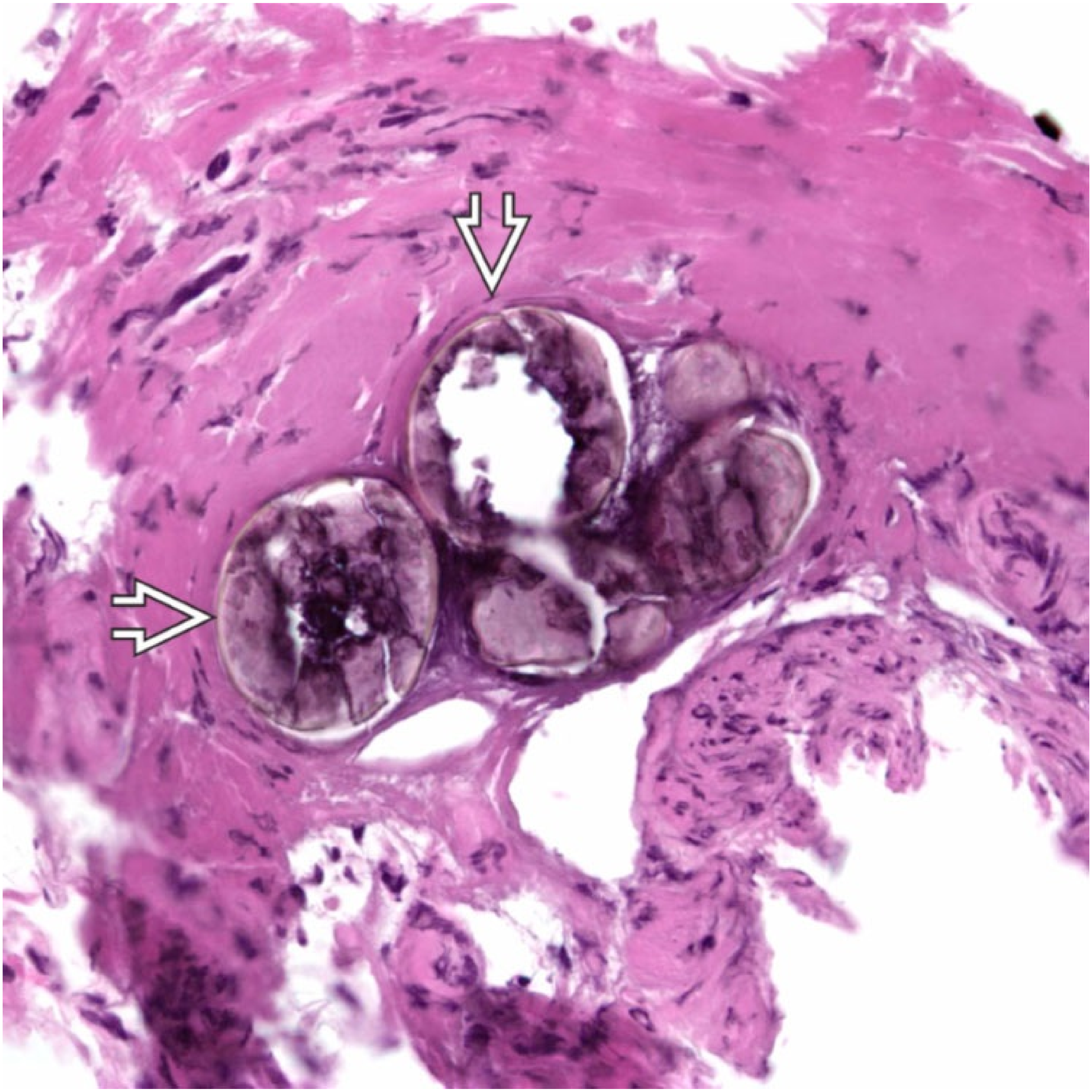
- *Clonorchis*, *Opisthorchis*, *Fasciola* : Variably present dilation of intrahepatic ducts, with mural thickening
  - Worms often visible to naked eye
- *Ascaris* : Large worms easily visible to naked eye
- Schistosoma: Fibrosis of bile ducts
- Protozoa: Cholangiopathy/stenosis of common bile duct

Microscopic

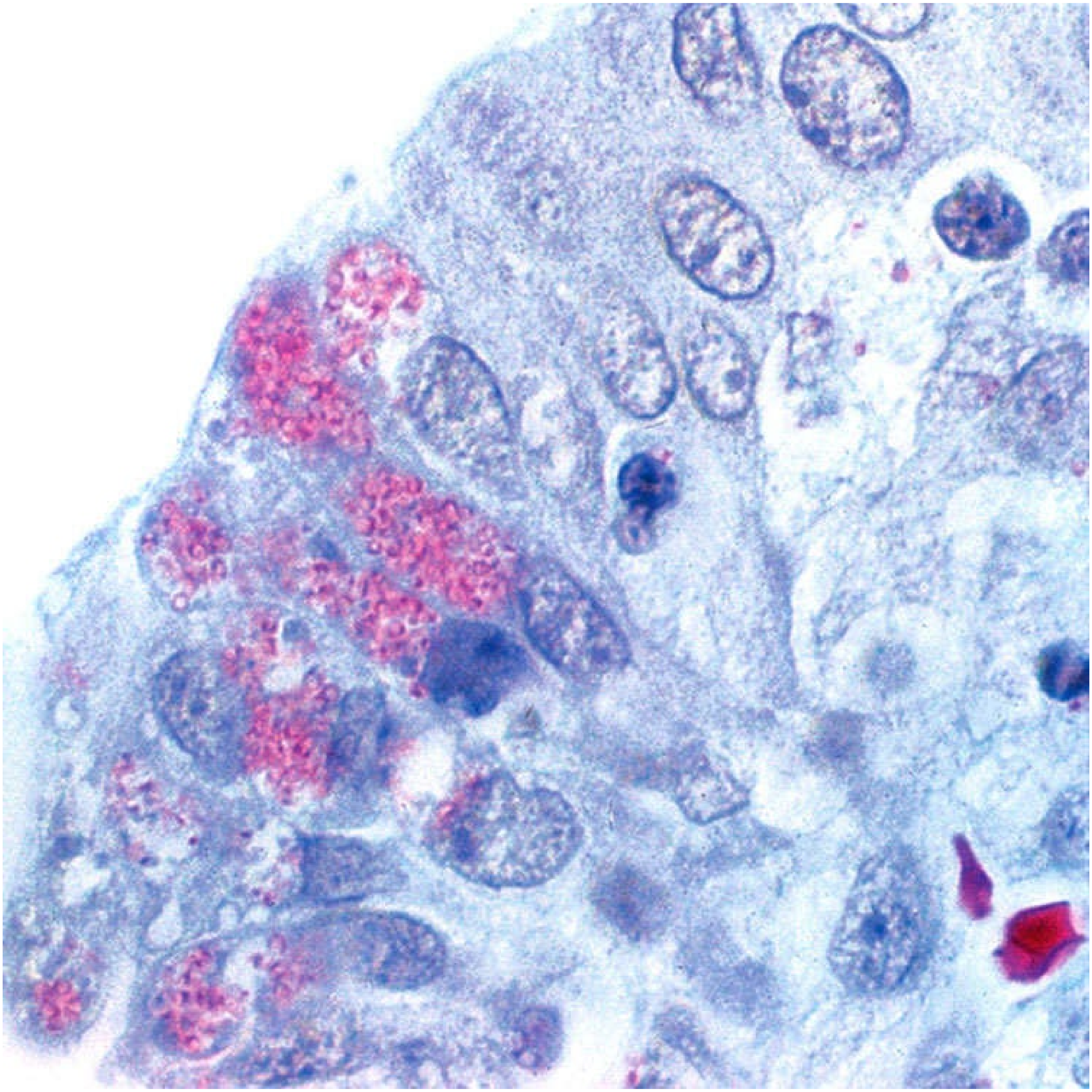
- Protozoa: Epithelial disarray, lymphocytic inflammation, organisms in epithelium
- Flukes: Inflammation of ducts with fibrosis, reactive epithelial changes

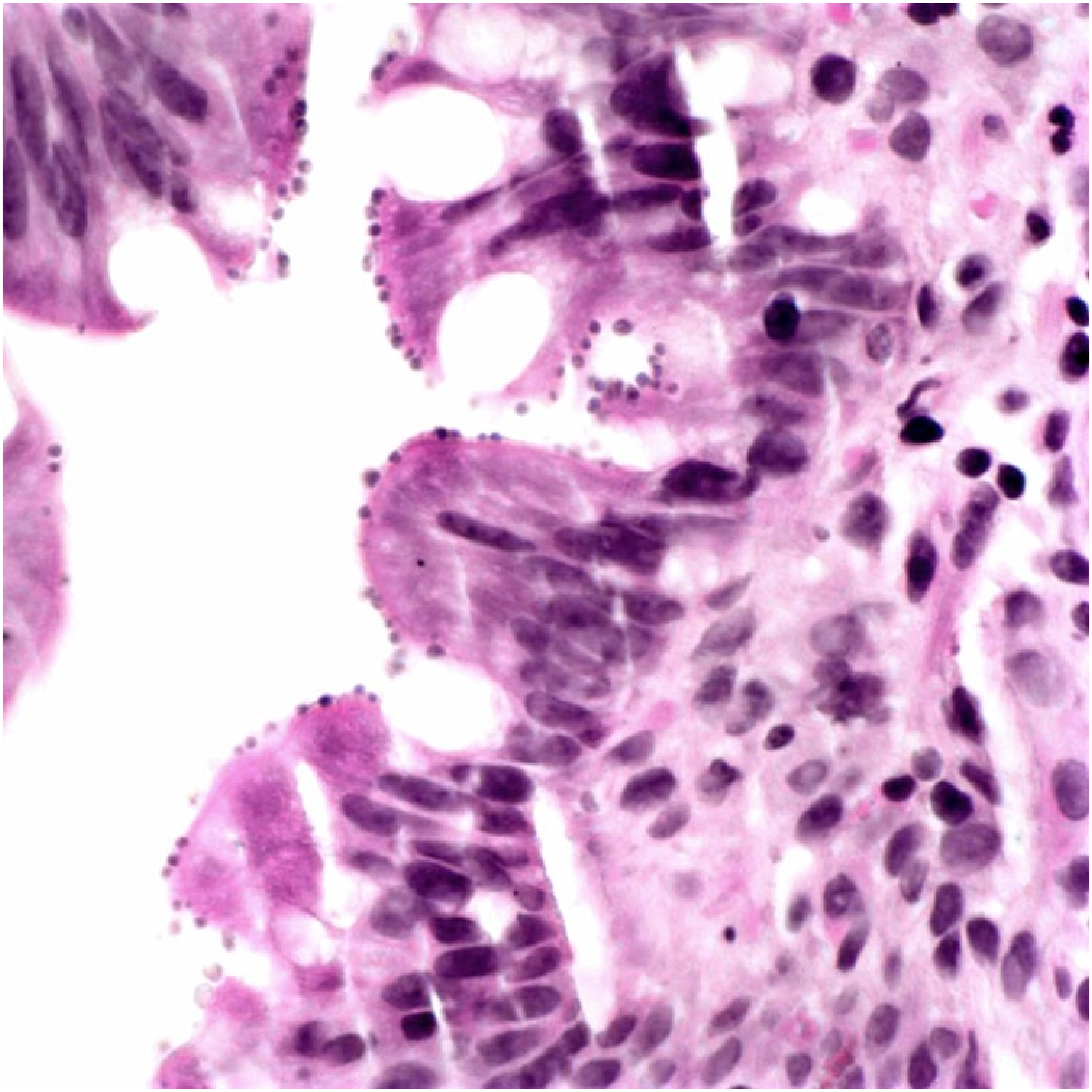


Liver Fluke
Liver flukes are flat, somewhat transparent, and tapered anteriorly. They have prominent oral and ventral suckers. (Courtesy J. Doss, MD.)



Schistosomiasis
Rarely, calcified schistosomal eggs ➾ are seen in the periductal connective tissue.


Microsporidia
High-power view of Microsporidia infection in the biliary tree shows the red spores within the cytoplasm of the epithelial cells.



Cryptosporidiosis
Cryptosporidia are round, basophilic protozoa with a unique location within the apical cytoplasm of epithelial cells.

TERMINOLOGY

Definitions

- Infection of bile ducts by parasite

ETIOLOGY/PATHOGENESIS

Protozoans

- *Cryptosporidium*, *Microsporidia*, *Cystoisospora* species

Helminths

- Trematodes
  - Liver flukes
  - – *Clonorchis sinensis*, *Opisthorchis* species, *Fasciola* species
- *Schistosoma* species (blood flukes)
- Nematodes
  - *Ascaris* species

CLINICAL ISSUES

Presentation

- Protozoans
  - Infection usually seen in context of AIDS (AIDS cholangiopathy)
  - – Also seen in transplant patients
  - – Occasionally seen in immunocompetent patients
- Gradual and regular stenosis of common bile duct with dilation of intrahepatic bile ducts
- – Some patients have irregularities of intrahepatic bile ducts that mimic primary sclerosing cholangitis (PSC)
- Symptoms include abdominal pain, occasionally low-grade fever; rarely jaundice
- *Clonorchis* and *Opisthorchis*
  - Endemic in many parts of Asia (*Clonorchis* and *O. viverrini*), Russia, and Eastern Europe (*O. felineus*)
  - Infection acquired from eating raw or undercooked fish, crawfish
  - Symptoms
    - – Right upper quadrant (RUQ) pain, fatigue, anorexia, diarrhea
    - – Growth retardation in children
  - Light infection may be asymptomatic
  - Complications include obstruction, cholangitis
- *Fasciola*
  - Primarily disease of farm animals; human infection acquired from eating contaminated watercress
  - Acute fascioliasis: Fever, hepatomegaly, peripheral eosinophilia
  - Chronic infection presents as biliary colic
- *Schistosoma* species (schistosomiasis)
  - May involve both intra- and extrahepatic bile ducts
  - Signs and symptoms of portal hypertension

- *Ascaris*
  - Duodenal infection that may involve bile ducts
  - Sudden onset of severe RUQ pain when worm enters duct

Laboratory Tests

- ± elevated bilirubin, alkaline phosphatase, transaminases

Treatment

- Cholangiopathy due to protozoal infection
  - Sphincterotomy to relieve obstruction and correct stenosis
  - Antiretroviral therapy may be helpful in AIDS patients
- Helminths usually treated with medical therapy

Prognosis

- Depends on specific infection and status of host
  - Sequelae of *Clonorchis*, *Opisthorchis* infection include cholangiocarcinoma, Oriental cholangiohepatitis
  - *Fasciola* not associated with malignancy

MACROSCOPIC

General Features

- Protozoans
  - Stenosis of common bile duct
- *Clonorchis*, *Opisthorchis*, *Fasciola* : Variably present dilation of intrahepatic ducts, with mural thickening
  - Worms are visible to naked eye
- *Schistosoma* species: Fibrosis of bile ducts (pipestem fibrosis)
- *Ascaris* : Large worms easily visible to naked eye

MICROSCOPIC

Histologic Features

- Protozoans
  - Epithelial disarray, lymphocytic inflammation; organisms present within epithelium
- *Opisthorchis* and *Clonorchis* : Epithelial desquamation followed by hyperplasia of epithelium and periductal mucus glands, periductal fibrosis
- *Fasciola* : Necrosis and hemorrhage of ducts with abscess formation, resulting in fibrosis
- *Schistosoma* : Vigorous fibroinflammatory response to dead eggs entraps bile ducts
  - Viable and nonviable eggs may rarely be seen in fibrous tissue adjacent to ducts

DIFFERENTIAL DIAGNOSIS

Primary Sclerosing Cholangitis

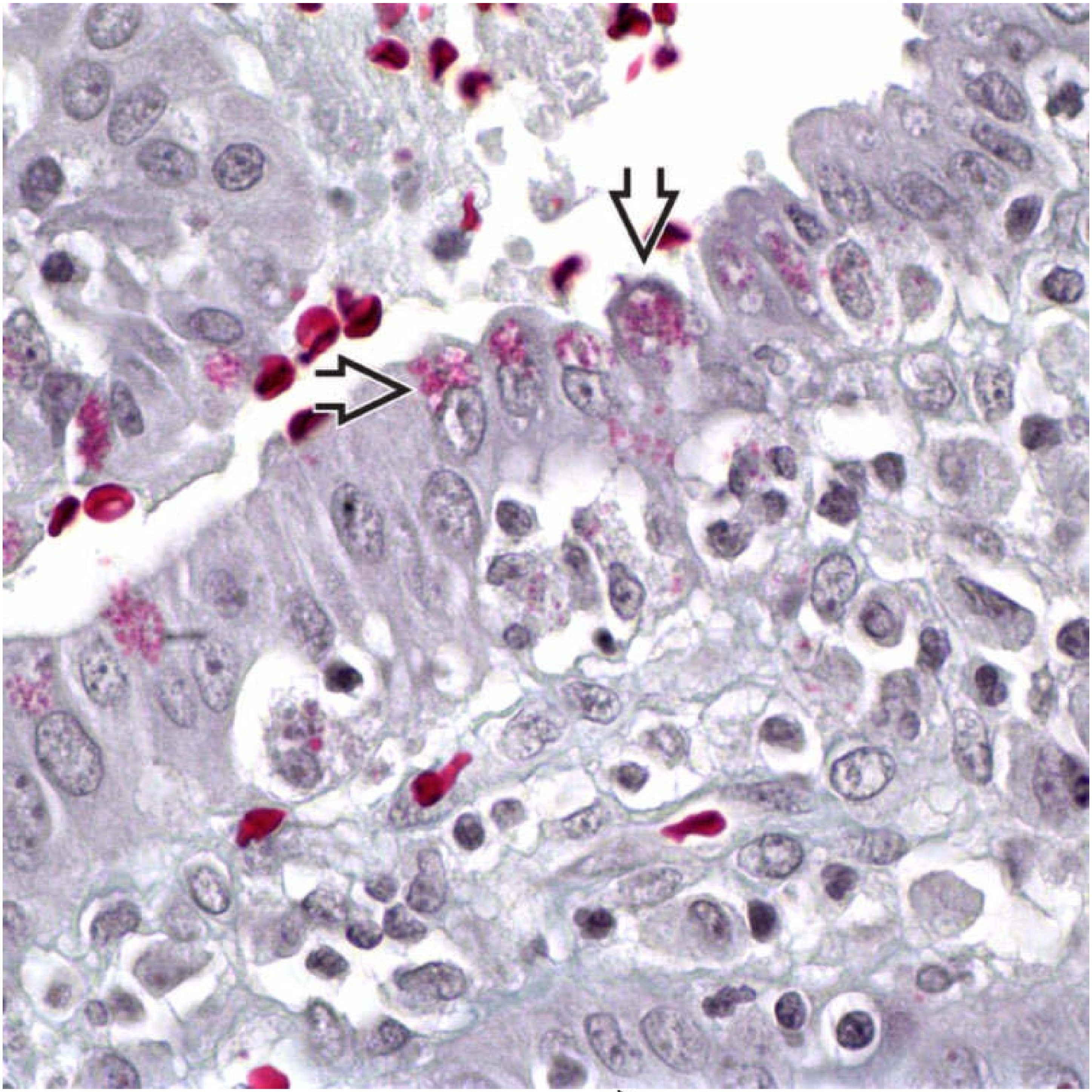
- Protozoal infection of biliary tree can mimic PSC radiographically

Other Causes of Large Bile Duct Obstruction

- Gallstones, neoplasms

Other Causes of Cholangitis

- Bacterial infection



The modified trichrome stain highlights Microsporidia (red) ➪ within the cytoplasm of biliary epithelium.

SELECTED REFERENCES

1. De Angelis, C, et al. An update on AIDS-related cholangiopathy. *Minerva Gastroenterol Dietol*. 2009; 55(1):79–82.
2. Walther, Z, et al. Isospora cholangiopathy: case study with histologic characterization and molecular confirmation. *Hum Pathol*. 2009; 40(9):1342–1346.
3. Brant, PE, et al. Anicteric cholangiopathy in schistosomiasis patients. *Acta Trop*. 2008; 108(2-3):218–221.
5. Chen, XM, et al. Cryptosporidiosis and the pathogenesis of AIDS-cholangiopathy. *Semin Liver Dis*. 2002; 22(3):277–289.

6. Carpenter, HA. Bacterial and parasitic cholangitis. *Mayo Clin Proc*. 1998; 73(5):473–478.
8. Forbes, A, et al. Natural history of AIDS related sclerosing cholangitis: a study of 20 cases. *Gut*. 1993; 34(1):116–121.
9. Pol, S, et al. Microsporidia infection in patients with the human immunodeficiency virus and unexplained cholangitis. *N Engl J Med*. 1993; 328(2):95–99.

4. Rana, SS, et al. Parasitic infestations of the biliary tract. *Curr Gastroenterol Rep*. 2007; 9(2):156–164.
7. Bouche, H, et al. AIDS-related cholangitis: diagnostic features and course in 15 patients. *J Hepatol*. 1993; 17(1):34–39.
10. Dowsett, JF, et al. Sclerosing cholangitis in acquired immunodeficiency syndrome. Case reports and review of the literature. *Scand J Gastroenterol*. 1988; 23(10):1267–1274.

SECTION 3
NONNEOPLASTIC AND INFLAMMATORY DISORDERS OF THE PANCREAS

OUTLINE

Acute Pancreatitis

KEY FACTS

Terminology

- Acute inflammation of pancreas

Etiology/Pathogenesis

- Gallstone and alcoholic pancreatitis account for 70-80% of cases

Clinical Issues

- Acute upper abdominal pain with nausea and vomiting
- Elevated serum amylase and lipase
- Treatment includes supportive care and infection prevention

Macroscopic

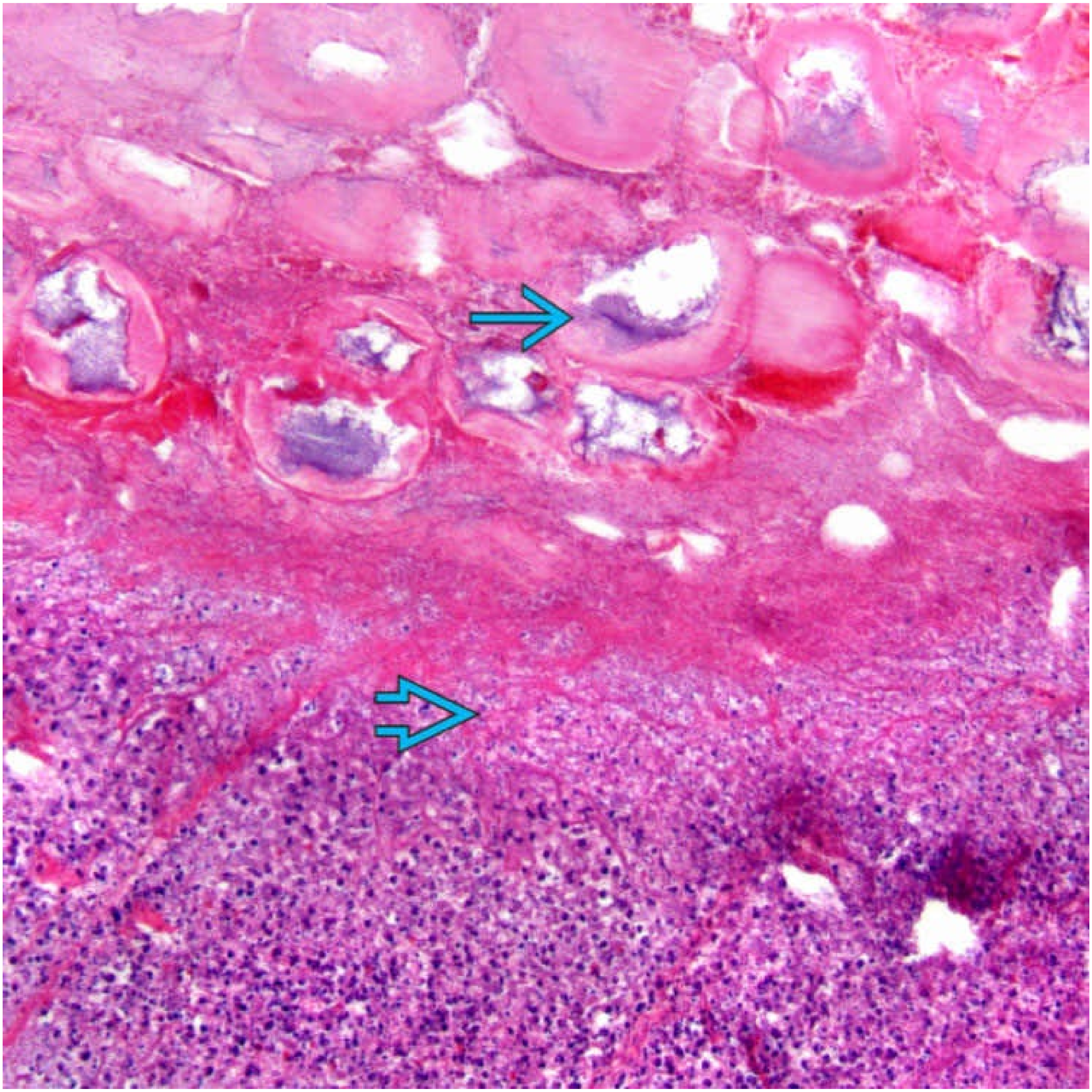
- Pancreas enlarged and swollen in mild pancreatitis
- Foci of fat necrosis (yellow-white, waxy or chalky consistency)
- Larger confluent areas of fat necrosis and parenchymal necrosis in severe necrotizing pancreatitis

Microscopic

- Severe acute pancreatitis
  - Large areas of fat necrosis along with variable parenchymal necrosis
  - Saponification
  - Hemorrhage, vascular thrombosis
- Mild acute pancreatitis is most often clinical (rather than morphologic) diagnosis
  - Spotty peripancreatic or perilobular fat necrosis and interstitial acute inflammation

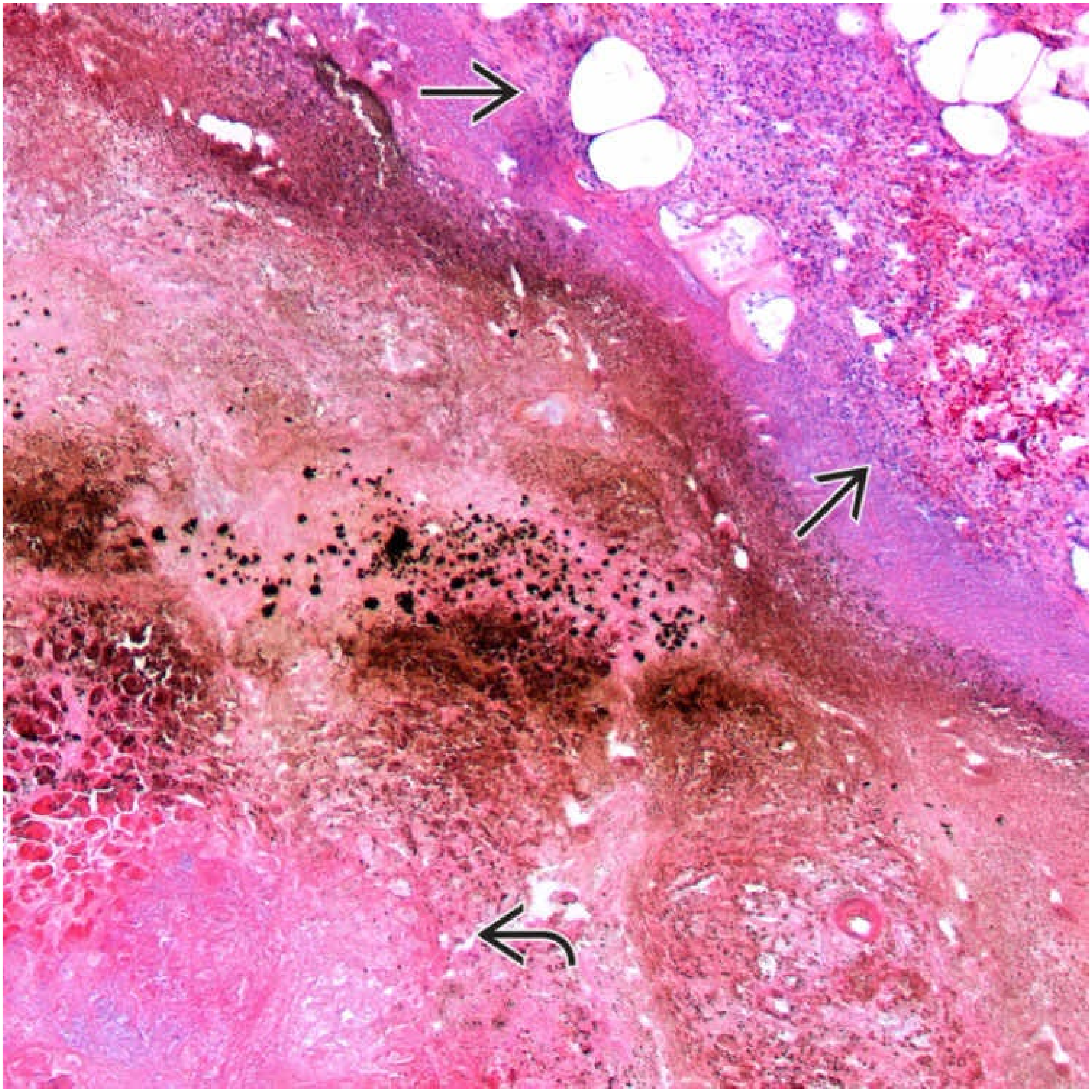
Top Differential Diagnoses

- Chronic pancreatitis
    - Fibrosis, chronic inflammation, lacks inflammatory component
- Autoimmune pancreatitis
    - Prominent lymphoplasmacytic infiltrate and storiform fibrosis

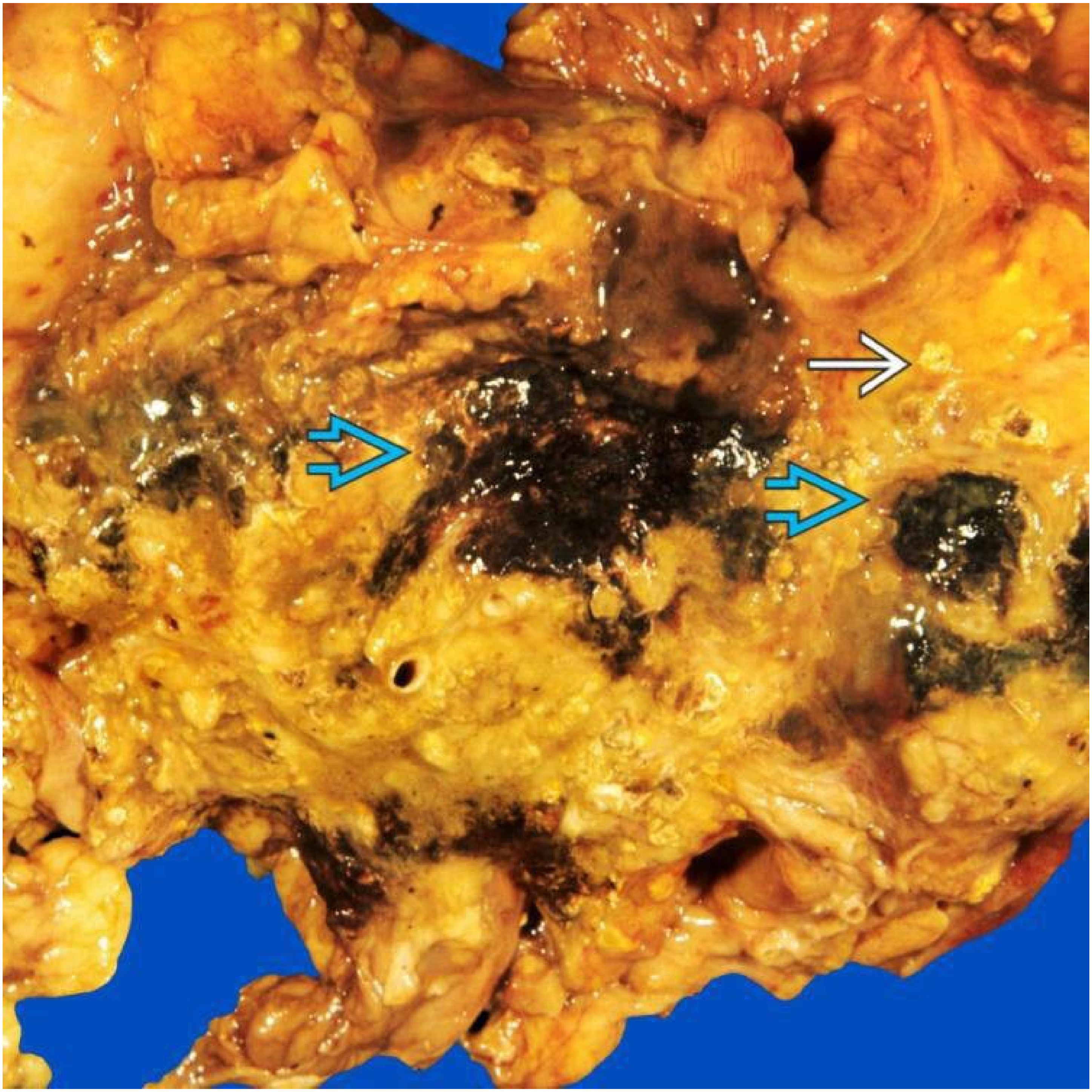


Acute Pancreatitis With Saponification

Pancreatic necrosis ⇨ and saponification of peripancreatic fat with calcification → are shown in a patient with acute pancreatitis.



Necrosis and Acute Inflammation
Trypsinogen activation is a key step in the development of acute pancreatitis. The release of digestive enzymes results in fat necrosis with acute inflammation → and pancreatic parenchymal necrosis ↶ .



Hemorrhage and Fat Necrosis
Gross examination reveals chalky white foci of fat necrosis and black areas of hemorrhage .

Acute Pancreatitis on CT
This CT shows severe acute necrotizing pancreatitis with heterogeneous and diminished enhancement of the pancreas ⇒ .

TERMINOLOGY

Definitions

- Acute inflammatory process involving pancreas

ETIOLOGY/PATHOGENESIS

Mechanical

- Gallstones, biliary sludge, periampullary diverticulum, neoplasms, duodenal stricture or obstruction
    - Gallstones most common cause, accounting for 35-60% of cases

Toxic

- Ethanol, methanol, scorpion venom, organophosphate poisoning
    - Alcohol is 2nd most common cause of acute pancreatitis overall

Trauma

- Blunt or penetrating abdominal injury, iatrogenic injury during procedure

Metabolic

- Hyperlipidemia type V and hypercalcemia

Vascular

- Ischemia, intraoperative hypotension, hemorrhagic shock, atheroembolism, vasculitis

Genetic

- Mutations of serine protease 1 gene (*PRSS1*), serine protease inhibitor Kazal type 1 (*SPINK1*), and cystic fibrosis transmembrane conductance regulator (*CFTR*)

Drug Induced

- Numerous drugs implicated

Infectious Agents

- Virus: Mumps, coxsackievirus, CMV, varicella-zoster, HSV, HIV
- Bacteria: *Mycoplasma*, *Legionella*, *Leptospira*, *Salmonella*
- Parasites: *Toxoplasma*, *Cryptosporidium*, *Ascaris*

Congenital

- Choledochocele type V

Miscellaneous

- Post ERCP, pregnancy, renal transplant, α-1-antitrypsin deficiency

Idiopathic

- 10-25% of patients have no identifiable cause

CLINICAL ISSUES

Epidemiology

- Occurs at any age
  - Most common in adults in 3rd to 6th decade of life
  - Occurrence during 1st decade suggests hereditary cause, infection, or trauma
- Gallstone pancreatitis more common in women between 50-60 years of age
- Alcoholic pancreatitis more common in men

Presentation

- Acute upper abdominal pain, nausea, vomiting

Laboratory Tests

- Elevated amylase and lipase

Natural History

- Mild cases usually recover within 5-7 days
  - Severe necrotizing pancreatitis associated with high rate of complication and significant mortality
  - Common sequelae are pancreatic abscess and pseudocyst

Treatment

- Supportive care, infection prevention

Prognosis

- Mortality in USA ranges from 2-10%
- Severe disease has higher mortality of 17%

Atlanta Classification

- Clinical classification; utility somewhat controversial
  - Mild (edematous and interstitial)
  - Severe (necrotizing)

MACROSCOPIC

Mild Acute Pancreatitis

- Enlarged and swollen with foci of fat necrosis (yellow-white, waxy or chalky consistency)

Severe Acute Pancreatitis

- Larger confluent areas of fat necrosis and parenchymal necrosis
- Hemorrhage can encase pancreas and simulate hematoma

MICROSCOPIC

Histologic Features

- Mild acute pancreatitis
  - Spotty peripancreatic or perilobular fat necrosis
  - Interstitial acute inflammation
  - Usually clinical rather than morphologic diagnosis
- Severe acute pancreatitis
  - Large areas of fat necrosis and variable pancreatic parenchymal necrosis
    - Saponification
  - Necrotic areas may have abundant neutrophils that can involve duct lumina
  - Viable acinar lumina may be widened and contain secretory material
  - Hemorrhage and usually venous thrombosis
  - Fat necrosis may extend to omentum, retroperitoneum, bone marrow, subcutaneous tissue

DIFFERENTIAL DIAGNOSIS

Chronic Pancreatitis

- Fibrosis, acinar atrophy, and chronic inflammation
- Lacks necrosis, acute inflammation

Autoimmune pancreatitis

- Prominent lymphoplasmacytic infiltrate, storiform fibrosis

SELECTED REFERENCES

1. Lankisch, PG, et al. Acute pancreatitis. *Lancet*. 2015; 386(9988):85–96.
2. Choi, JH, et al. Clinical relevance of the revised Atlanta classification focusing on severity stratification system. *Pancreatology*. 2014; 14(5):324–329.
3. Wu, BU, et al. Update in acute pancreatitis. *Curr Gastroenterol Rep*. 2010; 12(2):83–90.
4. Bradley, EL, 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. *Arch Surg*. 1993; 128(5):586–590.

Chronic Pancreatitis

KEY FACTS

Terminology

- Progressive inflammatory disorder of pancreas resulting in scarring, gland destruction, and functional impairment

Etiology/Pathogenesis

- Alcohol is by far most common cause of chronic pancreatitis (CP) in developed countries

Clinical Issues

- Abdominal pain is most common presenting symptom
- Steatorrhea
- Diabetes mellitus
- Weight loss

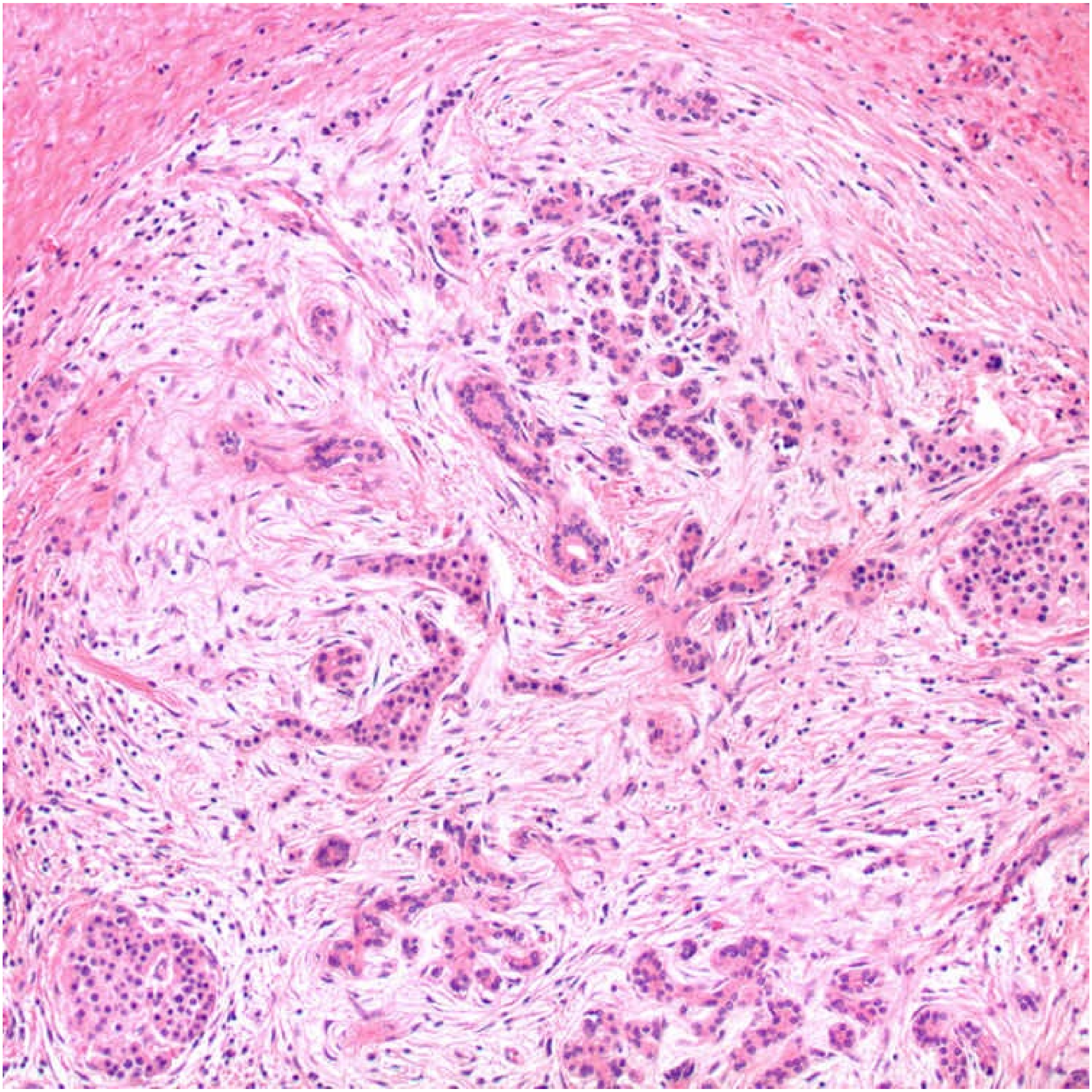
Macroscopic

- Firm, indurated, and fibrotic pancreas
  - Grossly affected area should be thoroughly sampled to exclude pancreatic adenocarcinoma, which can mimic CP grossly
  - Pancreatic adenocarcinoma and CP may coexist

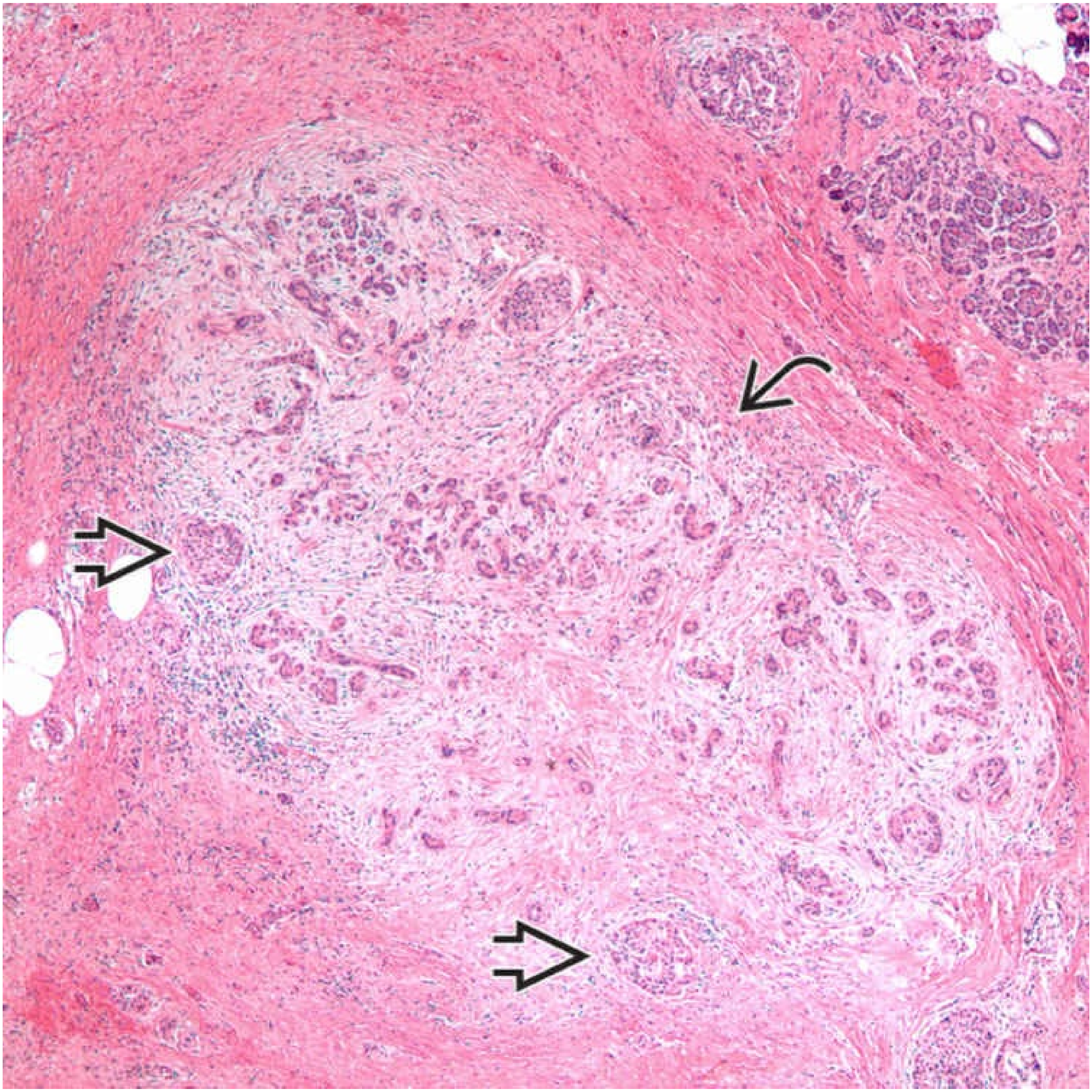
Microscopic

- Fibrosis and chronic inflammation
  - Variable extent and distribution of fibrosis
  - Irregular atrophy and obliteration of pancreatic acini and ducts
  - Retention of normal lobular pancreatic architecture
    - Lobular architecture aids histologic distinction from pancreatic adenocarcinoma
- Pancreatic duct alterations related to fibrosis and destruction
  - Duct epithelium may show atrophy, reactive, or hyperplastic changes

◦ Squamous, mucinous, or pyloric metaplasia
• Islets of Langerhans usually preserved, may show pseudohyperplasia

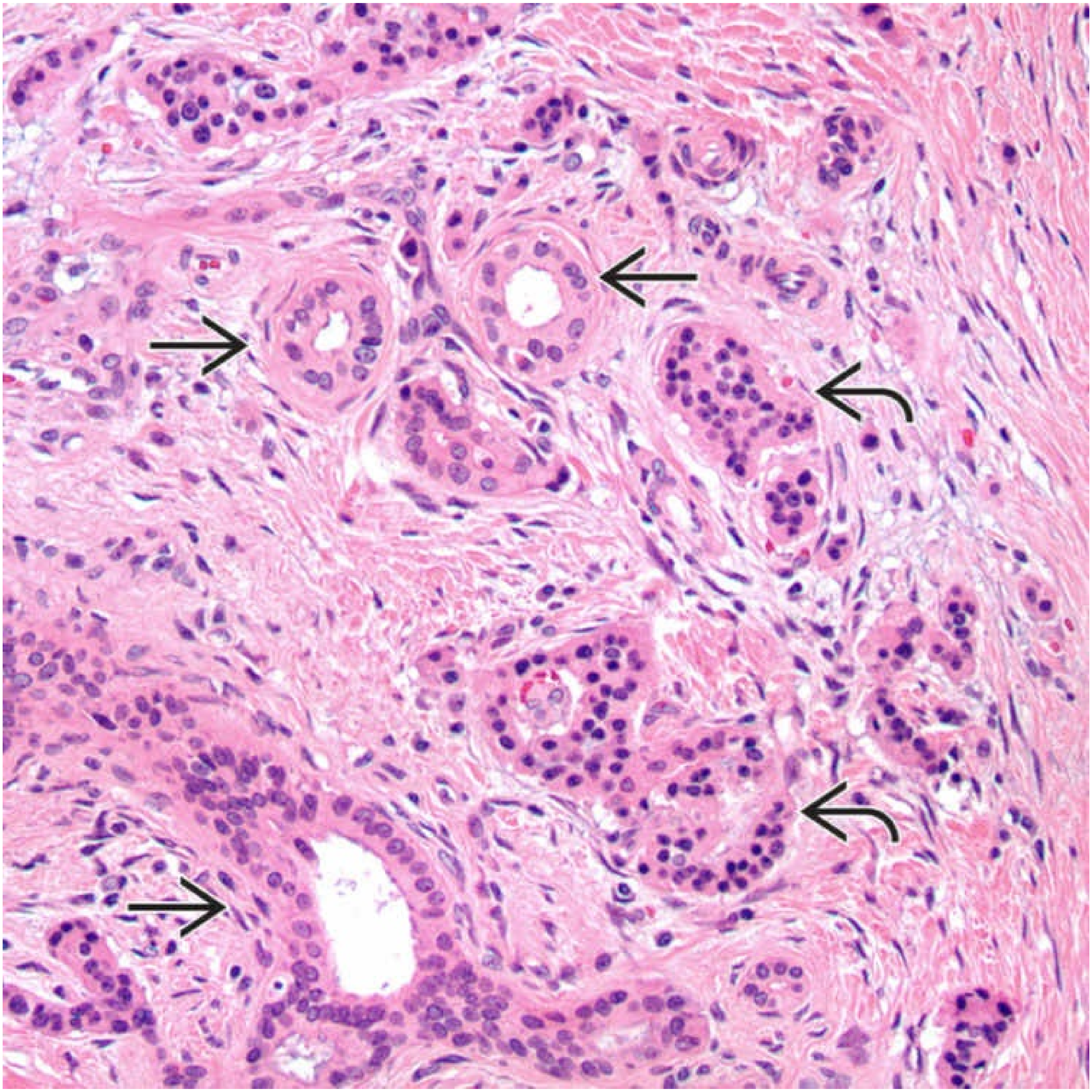


Fibrosis and Chronic Inflammation
The main features of chronic pancreatitis are fibrosis and chronic inflammation. Note the marked loss of acinar parenchyma. Residual islet cells and ductules are visible within the rounded contour of the lobule.



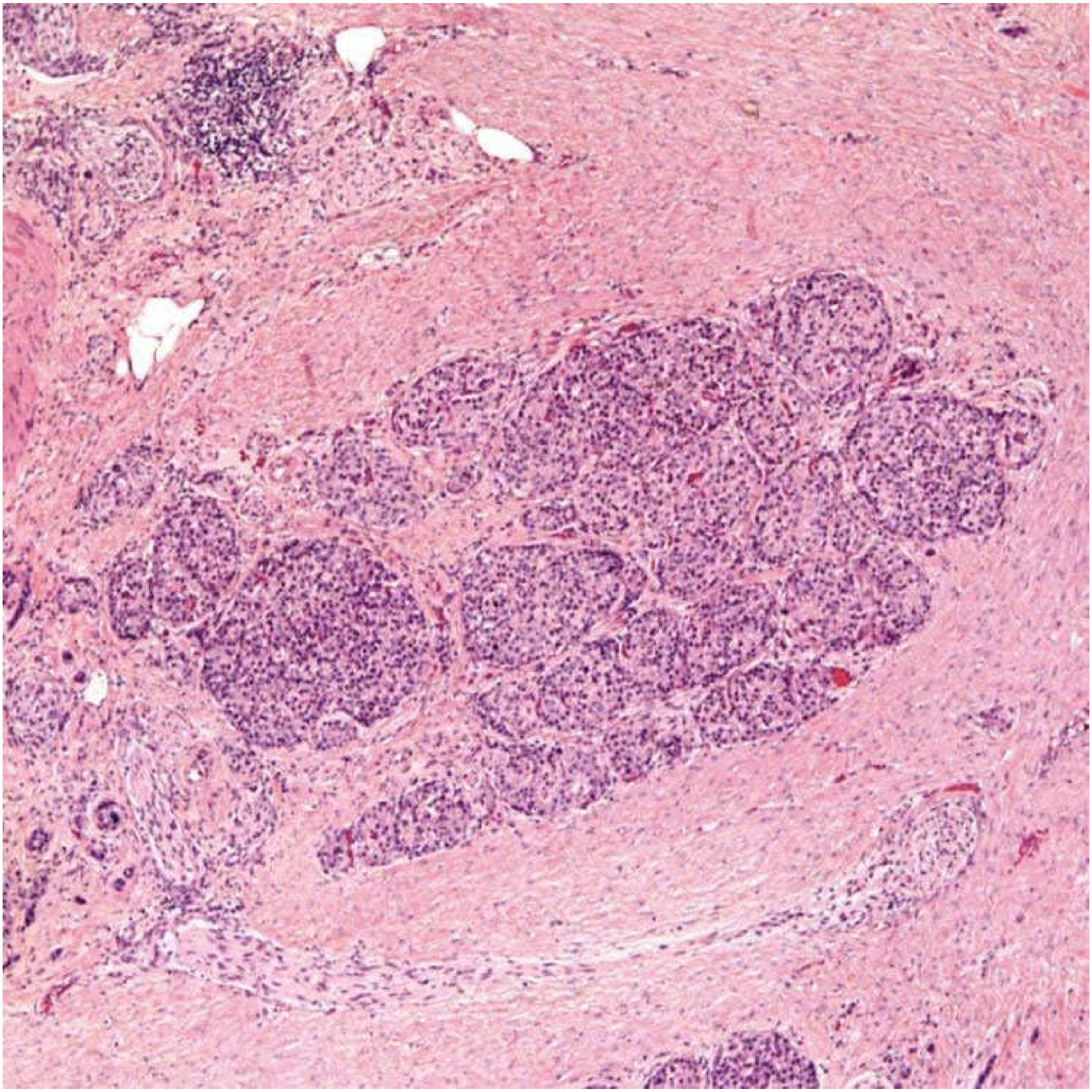
Preserved Lobular Architecture

In chronic pancreatitis, the normal lobular architecture is typically retained, and the rounded configuration of the lobule is apparent at low power. Note the fibrosis and loss of acinar parenchyma. Rare islets are still visible .



Atrophic Lobule With Acinar Loss

Atrophic lobules in chronic pancreatitis are characterized by lobular arrangements of small ducts →, fibrous tissue, and residual islet cells ↷. No residual acini are seen.


Islet Cell Pseudohyperplasia
Islet cell pseudohyperplasia, or proliferation and formation of cords and small clusters, is a common finding in chronic pancreatitis. Note the surrounding marked fibrosis and chronic inflammation. There is essentially no residual acinar parenchyma.

TERMINOLOGY

Abbreviations

• Chronic pancreatitis (CP)

Definitions

• Progressive inflammatory disorder of pancreas resulting in scarring, gland destruction, and functional

impairment

ETIOLOGY/PATHOGENESIS

Alcohol

- By far most common cause of CP in developed countries

Anatomic

- Duct obstruction
  - Stones or tumors involving head of pancreas lead to proximal duct dilatation, gland atrophy, and scarring
- Paraduodenal or “groove” pancreatitis

Metabolic

- Hypercalcemia
- Hyperlipidemia

Hereditary

- Autosomal dominant form
  - Several associated gene mutations described
  - Trypsinogen gene (*PRSS1*) accounts for 60-80% of hereditary CP cases
  - Cystic fibrosis transmembrane conductance regulator gene (*CFTR*)
  - Serine protease inhibitor Kazal type 1 gene (*SPINK1*)
  - Chymotrypsin C (*CTRC*)
- Presents during childhood with recurrent attacks of acute pancreatitis
- Complications similar to those seen in alcohol-related CP but at younger age

Eosinophilic

- Rare form of chronic pancreatitis with prominent eosinophilic infiltrate
  - May present as mass-forming process or with biliary obstruction
  - Often systemic process with peripheral eosinophilia and eosinophilias in other organs
  - May occur as primary disease or with other processes
  - Parasitic infection
  - Allergic process or hypersensitivity reaction
  - Associated with pancreatic carcinoma or inflammatory myofibroblastic tumor
  - Pancreatic allograft rejection

Tropical

- Aggressive form of juvenile pancreatitis occurring in tropical developing countries
- May be related to malnutrition, toxin exposure, &/or genetic predisposition

Other

- Also related to trauma, radiation injury, smoking, or medications
- Up to 25% of cases are idiopathic

CLINICAL ISSUES

Epidemiology

- Age
  - Alcohol-related CP usually affects adults > 40 years of age
  - Hereditary and tropical forms of CP present during childhood
- Sex
  - Alcohol-related CP more common in males than in females

Presentation

- Abdominal pain
  - Most common presenting symptom
- Steatorrhea
  - Associated with malabsorption due to impaired pancreatic enzyme secretion
- Diabetes mellitus, if advanced disease
- Weight loss
- Nausea
- Vomiting
- Often follows recurrent attacks of acute pancreatitis

Laboratory Tests

- May see elevated CA19-9

Natural History

- Chronic, progressive disease leading to permanent loss of pancreatic function
  - Loss of pancreatic enzyme secretions leads to malabsorption and steatorrhea
  - Pancreatic endocrine insufficiency
    - Diabetes more common in late disease
- Symptoms may wax and wane over course of disease
- Complications of advanced disease
  - Portal vein thrombosis
  - Splenic vein thrombosis
  - Jaundice
  - Pancreatic ascites
  - Pancreatic pseudocysts

Treatment

- Surgical approaches
  - Whipple pancreaticoduodenectomy
  - Pancreatic duct drainage procedure
  - Local or duodenum-preserving resection of pancreatic head
- Drugs
  - Pancreatic enzyme replacement aids intestinal absorption
- Pain management
  - Medical therapy
  - Celiac nerve block
- Diabetes treatment as needed with insulin and diet
- Dietary management
  - Low-fat meals
  - Frequent small meals may be better tolerated than less frequent, larger meals
- Stop offending agent (if identifiable)
  - Discontinue alcohol use
  - If obstructive CP, remove source of obstruction
    - Gallstones may be removed by endoscopic retrograde cholangiopancreatography (ERCP)
    - Sphincterotomy or balloon dilatation can relieve duct obstruction
    - Stent may be placed to maintain pancreatic duct opening

Prognosis

- CP is risk factor for pancreatic cancer
  - Lifetime risk varies
  - Patients with hereditary pancreatitis have 40% lifetime pancreatic cancer risk

IMAGING

Ultrasonographic Findings

- Pancreatic stones evident

CT Findings

- Intrapancreatic calcifications

ERCP Findings

- Irregular, dilated pancreatic duct and branches
- May reveal source of obstructive pancreatitis

MACROSCOPIC

General Features

- Findings may be diffuse, focal, or segmental
  - Usually, affected area is enlarged but may be shrunken in advanced CP
- Firm, indurated, and fibrotic pancreas
- Cystically dilated pancreatic ducts
  - May contain calcified protein concretions
- Pseudocysts may be evident
  - Variably sized, thick-walled cysts containing blood and necrotic debris

MICROSCOPIC

Histologic Features

- Irregular atrophy and obliteration of pancreatic acini and ducts
  - Results in overall loss of acinar tissue
- Retention of normal lobular pancreatic architecture
  - Rounded configuration of lobules preserved
- Pancreatic duct alterations related to fibrosis and destruction
  - Results in duct ectasia and saccular dilatations
  - Duct epithelium may show atrophy, reactive, or hyperplastic changes
    - Reactive epithelial cells show mild nuclear enlargement
  - Ducts may show spectrum of reactive alterations or metaplasia
    - Squamous metaplasia
    - Mucous cell metaplasia
    - Pyloric gland metaplasia
- Variable extent and distribution of fibrosis
  - Occurs around ducts and within & between lobules
- Chronic inflammation usually mild
- Islets of Langerhans usually relatively well preserved
  - Islets may become lost or atrophic in advanced CP
  - May also show pseudohyperplasia as result of parenchymal loss

DIFFERENTIAL DIAGNOSIS

Pancreatic Adenocarcinoma

- Invasive growth pattern vs. retained lobular architecture
  - Adenocarcinoma has irregularly distributed glands with infiltrative growth pattern
  - CP retains lobular pancreatic architecture
  - Perineural invasion and angiolymphatic space invasion are features of malignancy
  - Islet cells in CP may wrap around nerves, simulating malignancy
- Neoplastic glands are irregular, vs. round or tubular glands in CP with minimal branching
  - Individual malignant-appearing cells are feature of adenocarcinoma
  - Necrotic debris may be seen in malignant glands, but should not be seen in residual ducts in CP

  - Residual islet cells may appear singly or in irregular clusters, and should not be overinterpreted as evidence of cancer
- Cytologic features of malignancy
  - Nuclei are larger, more irregular, more hyperchromatic in adenocarcinoma, and show greater variation in size
  - Mitotic activity and atypical mitotic features are absent in CP

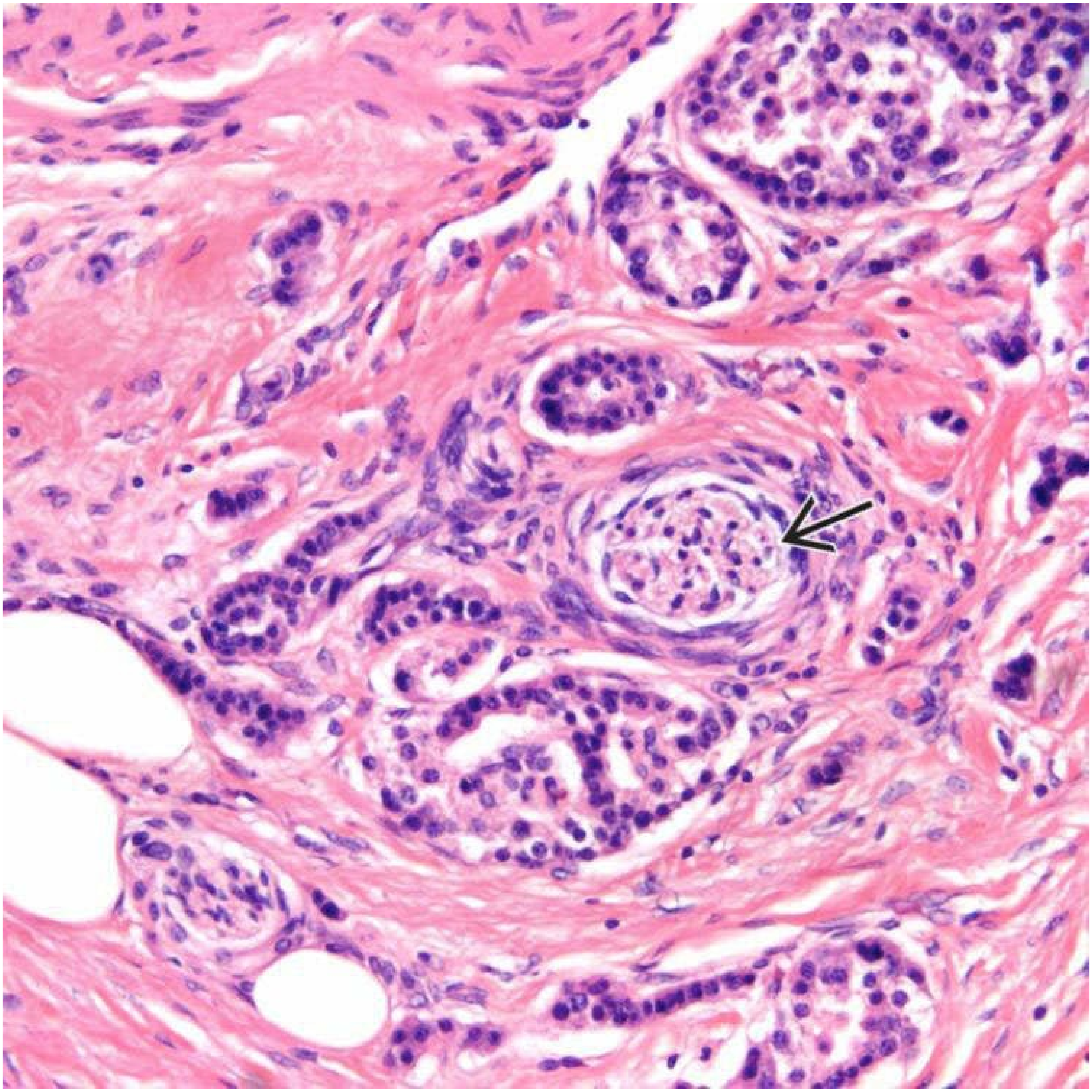
Autoimmune Pancreatitis

- More densely cellular inflammatory infiltrates than CP
  - Periductal inflammation consisting of large numbers of lymphocytes and IgG4(+) plasma cells
  – Injury and destruction of duct epithelium
  - Obliterative phlebitis of small to medium-sized veins in most cases (can be highlighted with elastic stain)
- Serum IgG4 level elevated in most patients

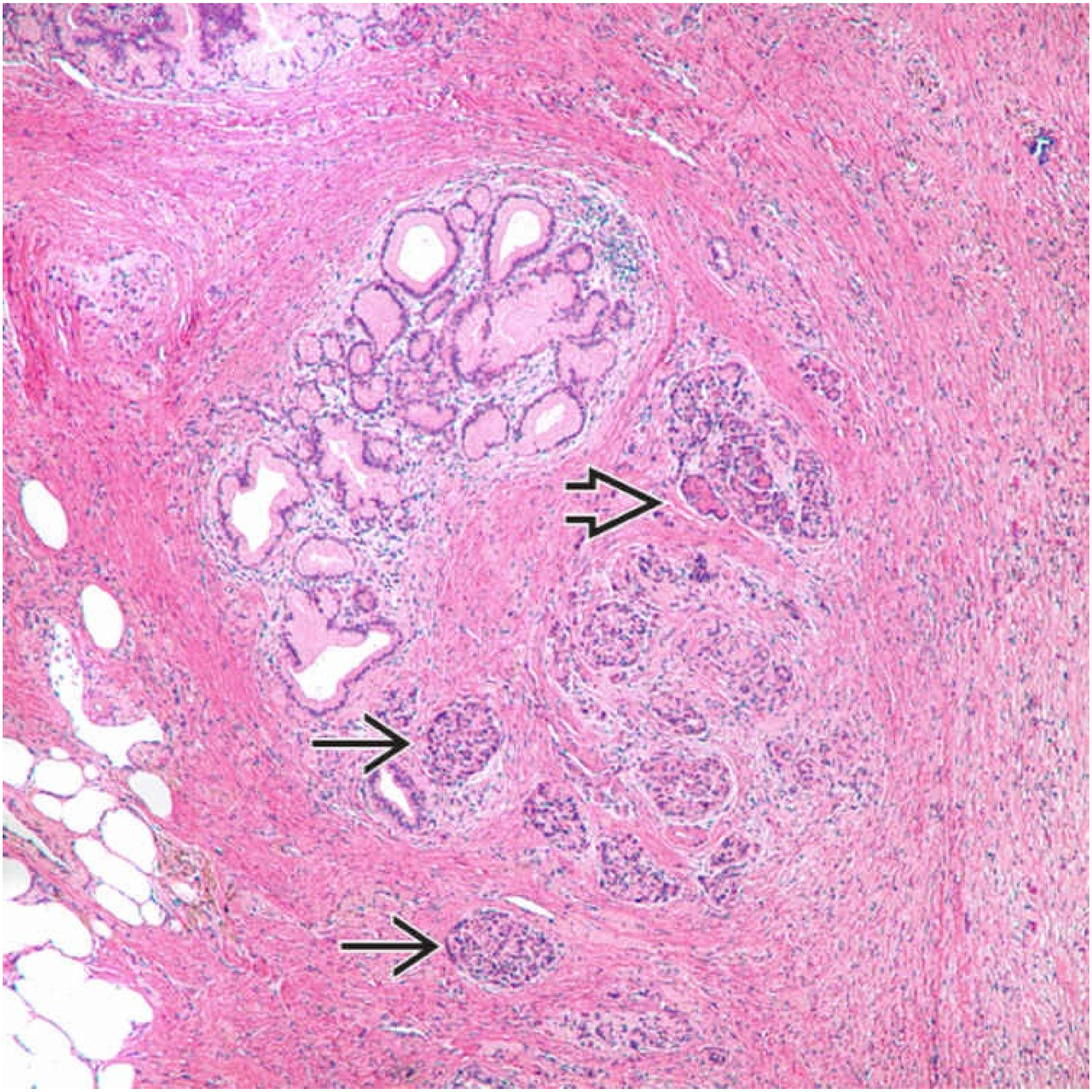
DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Dense parenchymal fibrosis may mimic neoplasm grossly
- Lobular architecture aids histologic distinction from pancreatic adenocarcinoma

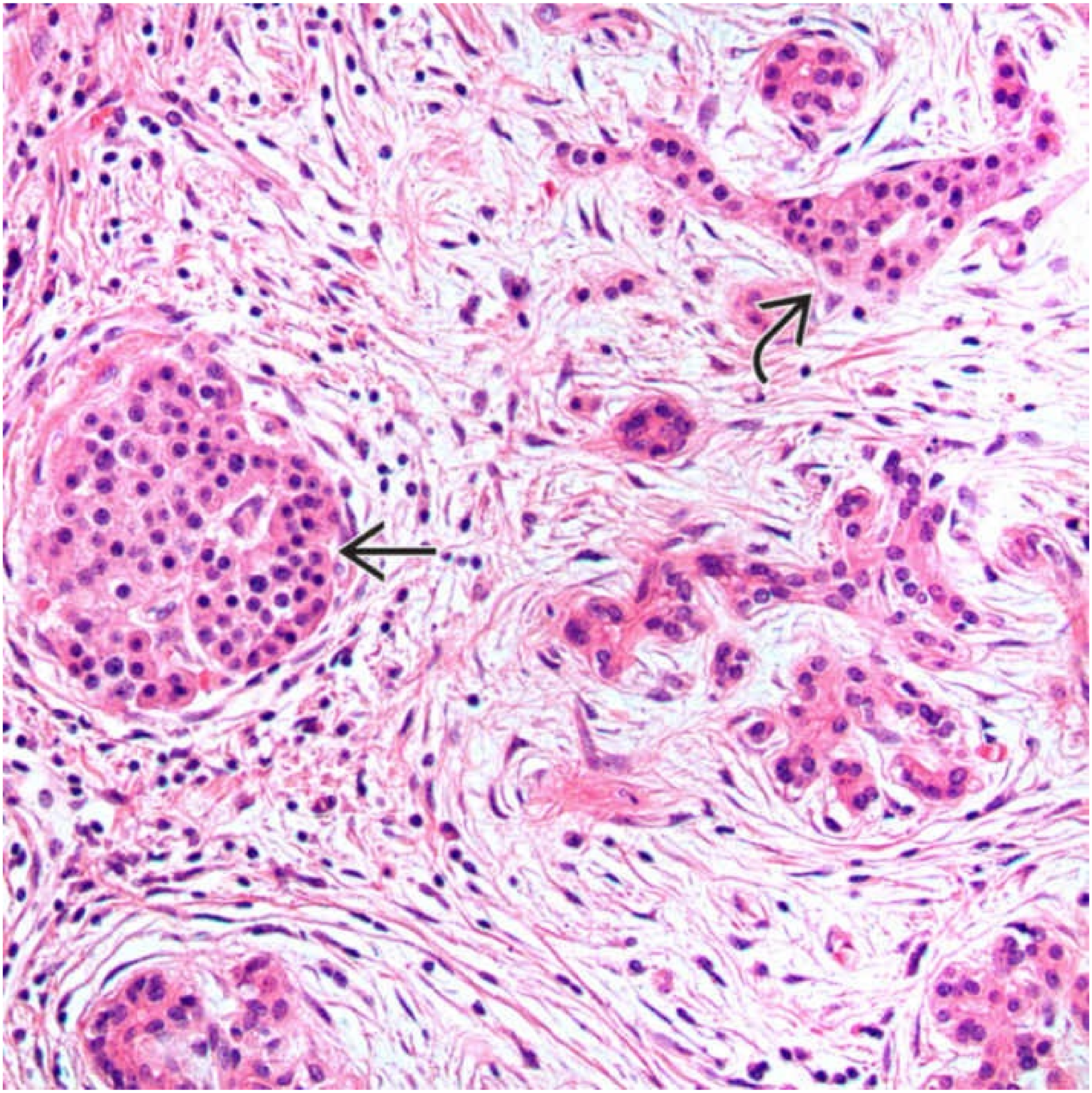


Perineural Islet Cells
Islet cells in chronic pancreatitis can surround nerves →, mimicking a malignant neoplasm.



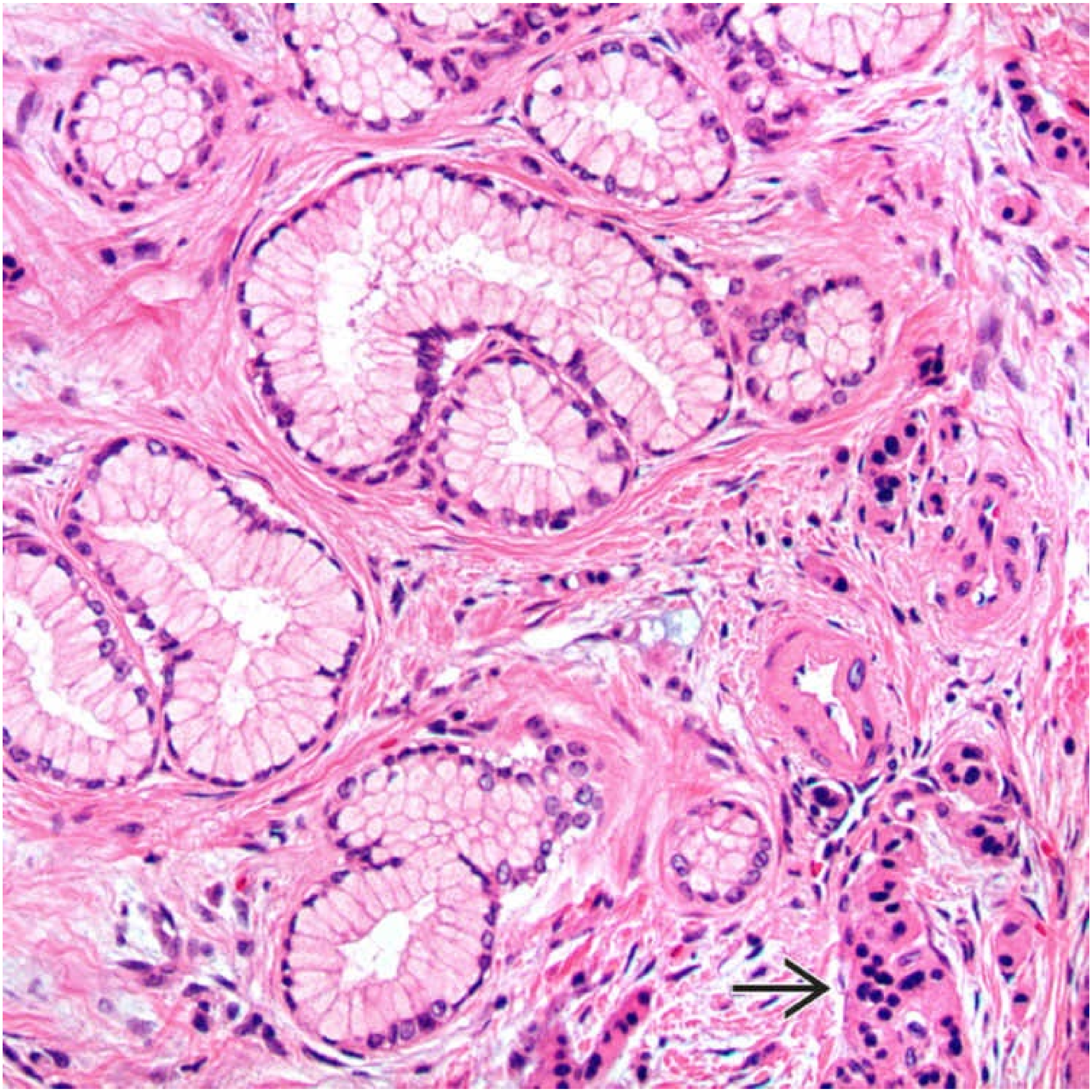
Retained Lobular Architecture

At low power, retention of the normal lobular architecture in chronic pancreatitis is visible. Residual islets of Langerhans → are present, but there are only focal residual acini ⇨. Fibrosis is prominent.

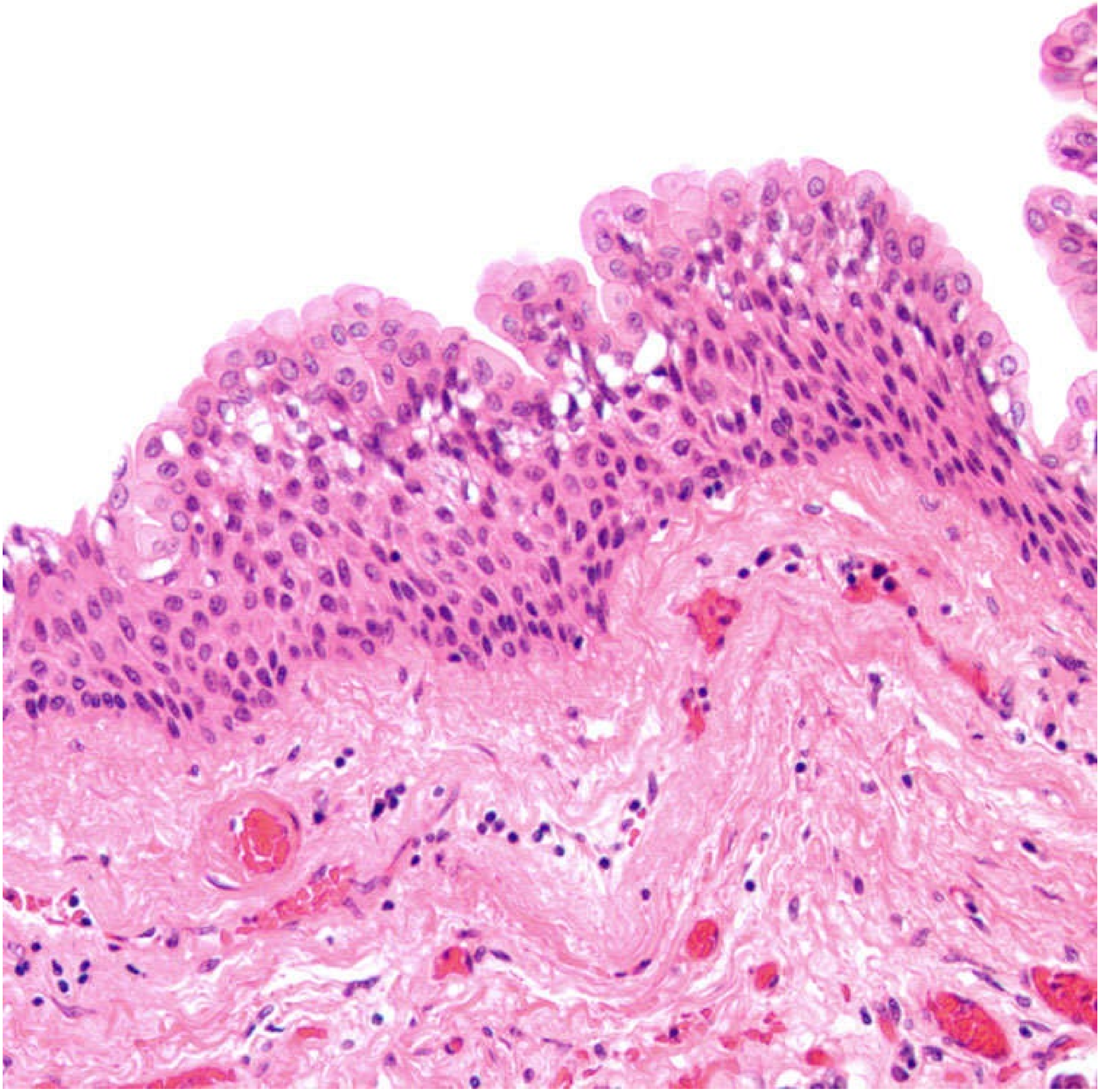


Fibrosis and Mild Chronic Inflammation

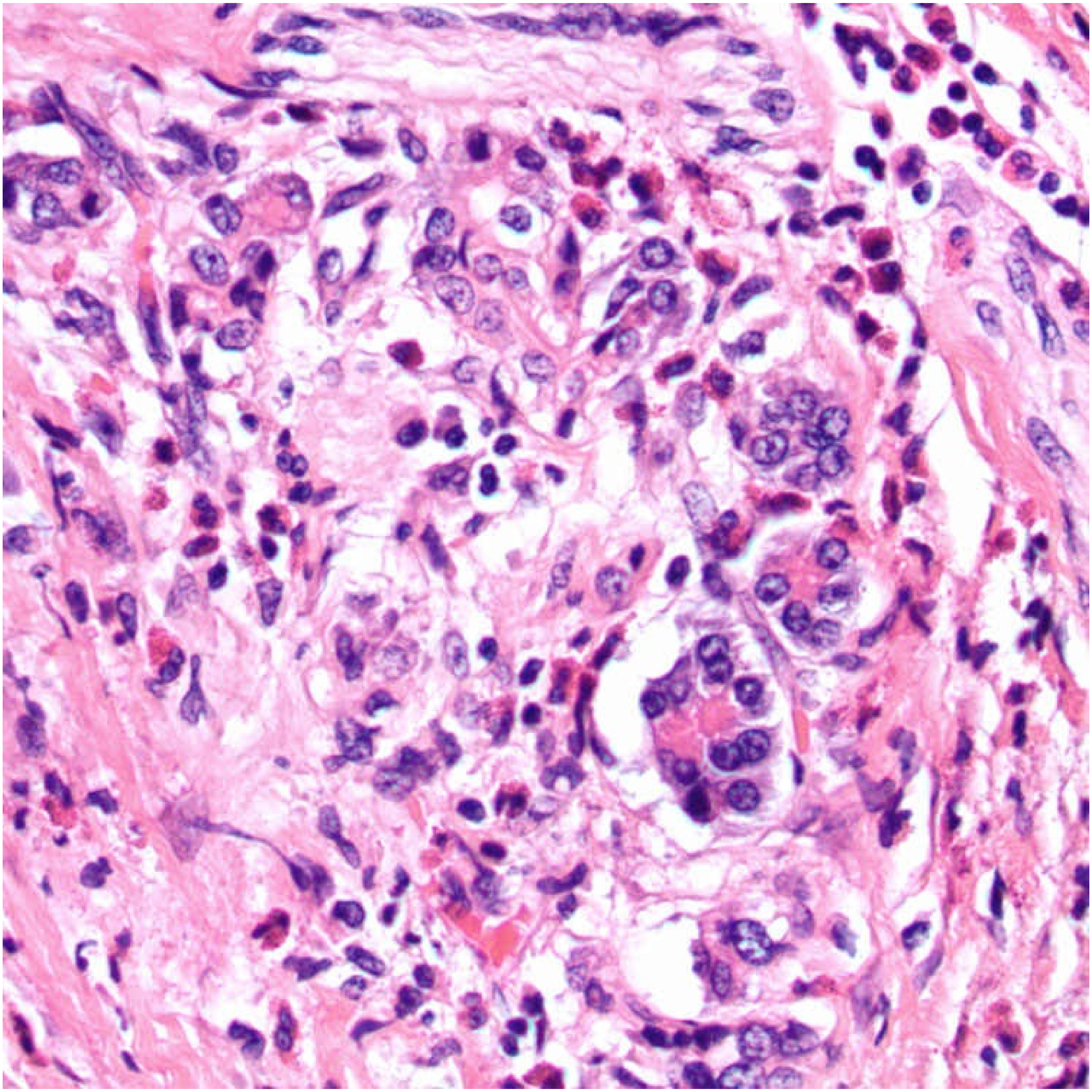
This micrograph illustrates fibrosis and mild chronic inflammation surrounding small pancreatic duct branches ↷ and preserved islets of Langerhans →. No residual acinar parenchyma is seen.



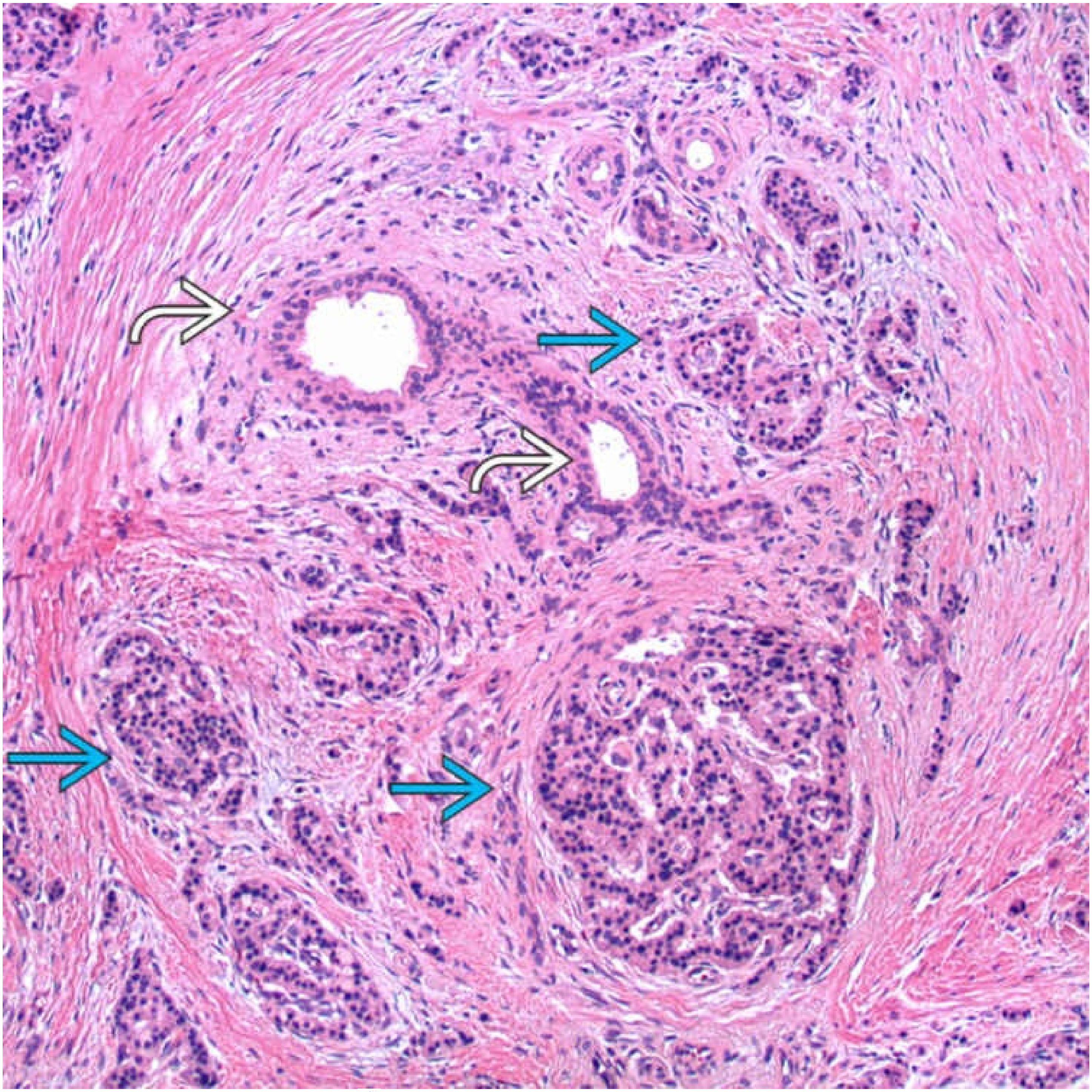
Mucinous Metaplasia of Pancreatic Ducts
Mucinous metaplasia is seen in small pancreatic duct branches in a case of chronic pancreatitis. Residual islet cells are also seen → .



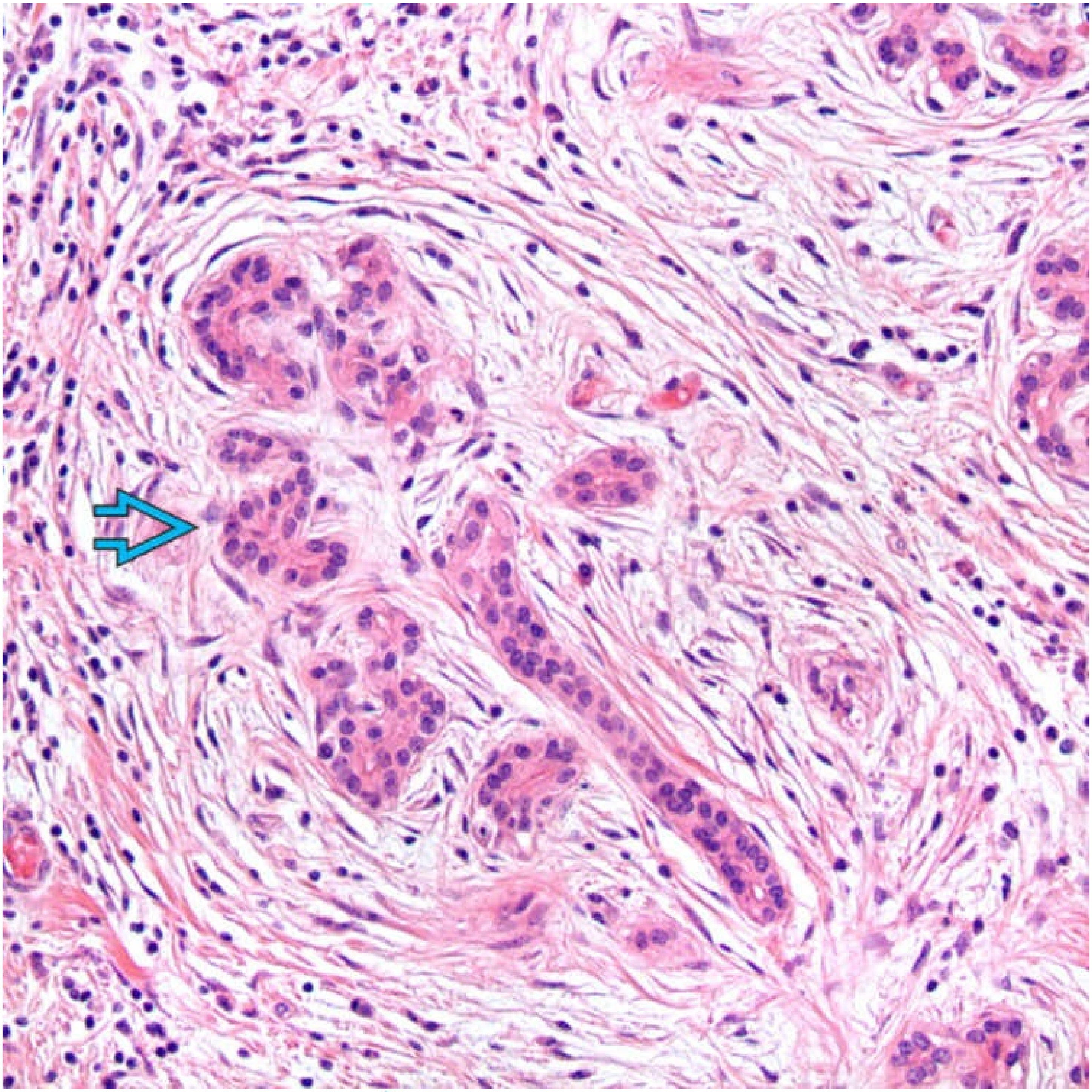
Squamous Metaplasia of Pancreatic Ducts
The ductal epithelium in chronic pancreatitis may show squamous metaplasia.



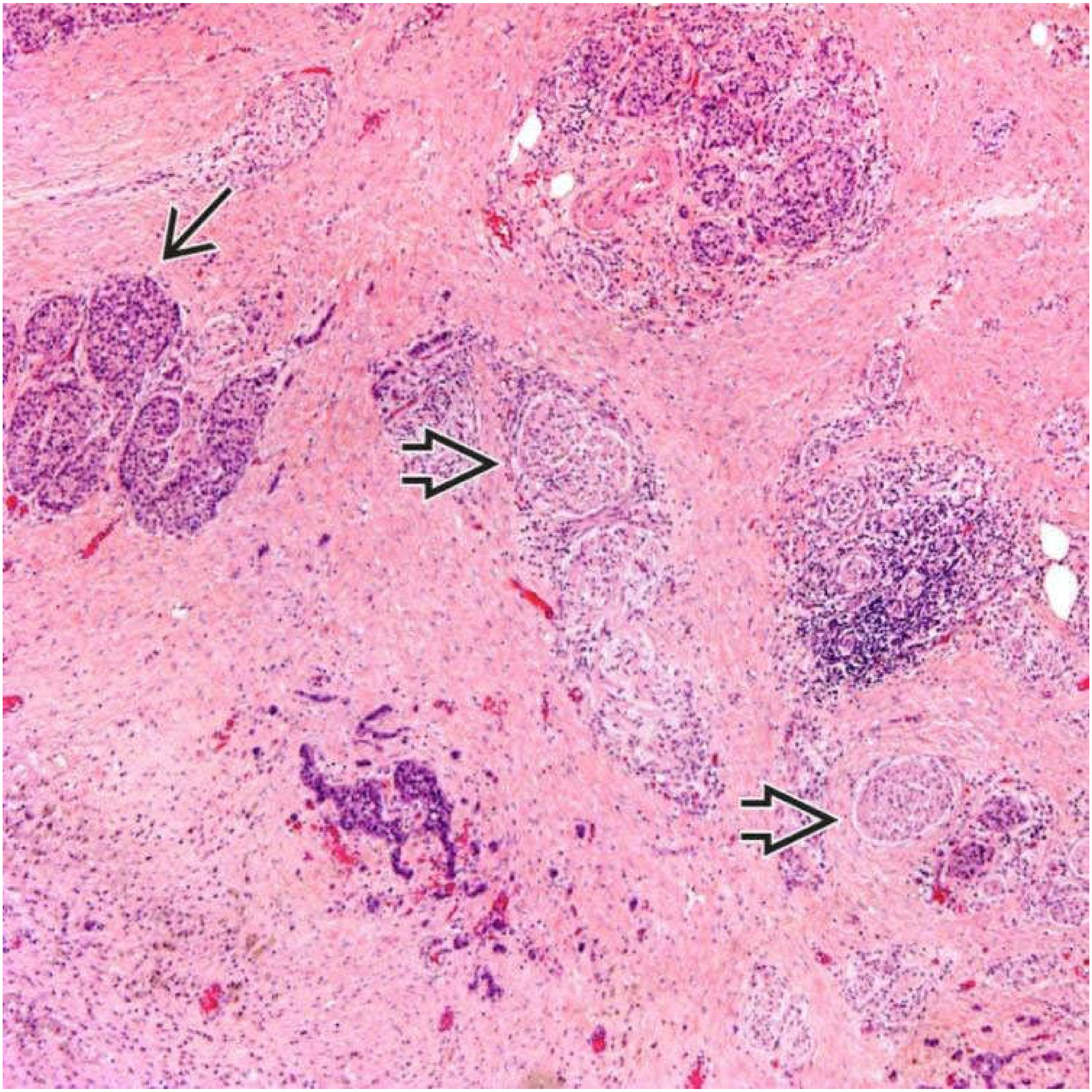
Eosinophilic Pancreatitis
This higher power photograph illustrates eosinophilic infiltrates and acinar injury in eosinophilic pancreatitis.



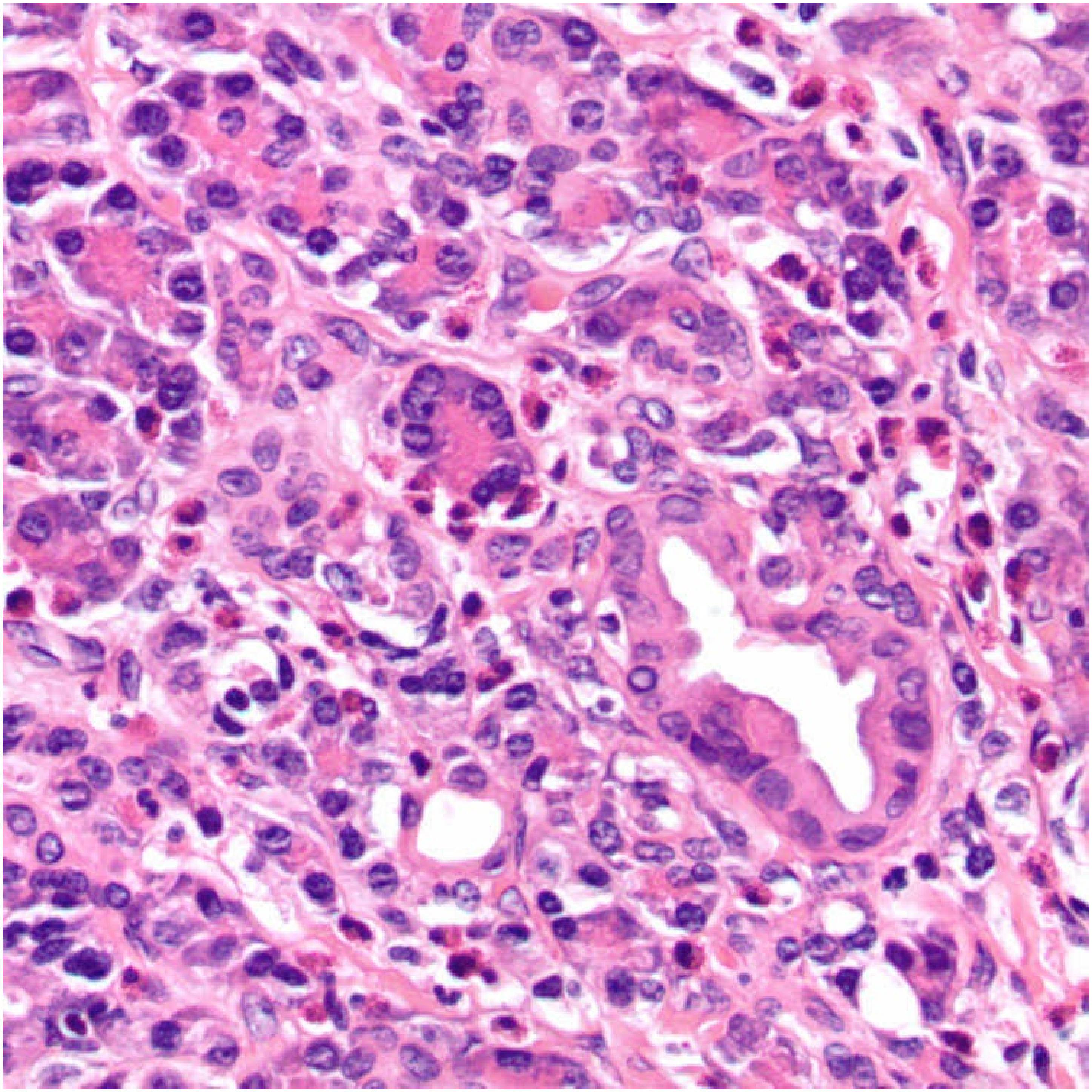
Residual islets of Langerhans appear prominent in this atrophic lobule. The acinar parenchyma is gone, leaving behind pancreatic duct branches and islet cells in a background of fibrosis.



Compressed pancreatic ducts are present within fibrous stroma. There is surrounding chronic inflammation.



The main features of chronic pancreatitis are fibrosis and chronic inflammation. Note the marked loss of acinar parenchyma. Residual nerves may be prominent ➩, and residual islet cells may form cords or small clusters → .


Prominent eosinophilic infiltrates and associated acinar injury are features of eosinophilic pancreatitis.

SELECTED REFERENCES

1. DiMagno, EP, et al. Chronic pancreatitis: landmark papers, management decisions, and future. *Pancreas*. 2016; 45(5):641–650.
2. Ito, T, et al. Evidence-based clinical practice guidelines for chronic pancreatitis 2015. *J Gastroenterol*. 2016; 51(2):85–92.
3. Majumder, S, et al. Chronic pancreatitis. *Lancet*. 2016; 387(10031):1957–1966.
6. Tian, L, et al. Eosinophilic pancreatitis: three case reports and literature review. *Mol Clin Oncol*. 2016; 4(4):559–562.
7. Bledsoe, JR, et al. Difficult diagnostic problems in pancreatobiliary neoplasia. *Arch Pathol Lab*

Med. 2015; 139(7):848–857.
8. Whitcomb, DC. Genetic aspects of pancreatitis. *Annu Rev Med*. 2010; 61:413–424.
10. Klöppel, G, et al. Chronic pancreatitis and the differential diagnosis versus pancreatic cancer. *Arch Pathol Lab Med*. 2009; 133(3):382–387.
11. Klöppel, G. Chronic pancreatitis, pseudotumors and other tumor-like lesions. *Mod Pathol*. 2007; 20(Suppl 1):S113–S131.

4. Palermo, JJ, et al. Genophenotypic analysis of pediatric patients with acute recurrent and chronic pancreatitis. *Pancreas*. 2016; 45(9):1347–1352.
5. Setiawan, VW, et al. Prospective study of alcohol drinking, smoking, and pancreatitis: The Multiethnic Cohort. *Pancreas*. 2016; 45(6):819–825.
9. Gaisano, HY, et al. New insights into the mechanisms of pancreatitis. *Gastroenterology*. 2009; 136(7):2040–2044.

Autoimmune Pancreatitis

KEY FACTS

Terminology

- Fibroinflammatory disease of presumed autoimmune etiology that affects pancreas
  - Often associated with elevated serum IgG4
  - Similar fibroinflammatory process often affects other organs such as bile ducts, salivary glands, retroperitoneum, and lymph nodes
- Associated with many other autoimmune diseases; ANA often positive

Clinical Issues

- Nonspecific: Jaundice, weight loss, vague abdominal pain
  - Elevated serum IgG4 (not invariably present, and not diagnostic of autoimmune pancreatitis)
  - More common in type 1 than type 2 AIP
- Steroid therapy is usually very effective
  - Recurrence reported in 6-26%
- Often mimics pancreatic adenocarcinoma clinically and radiographically

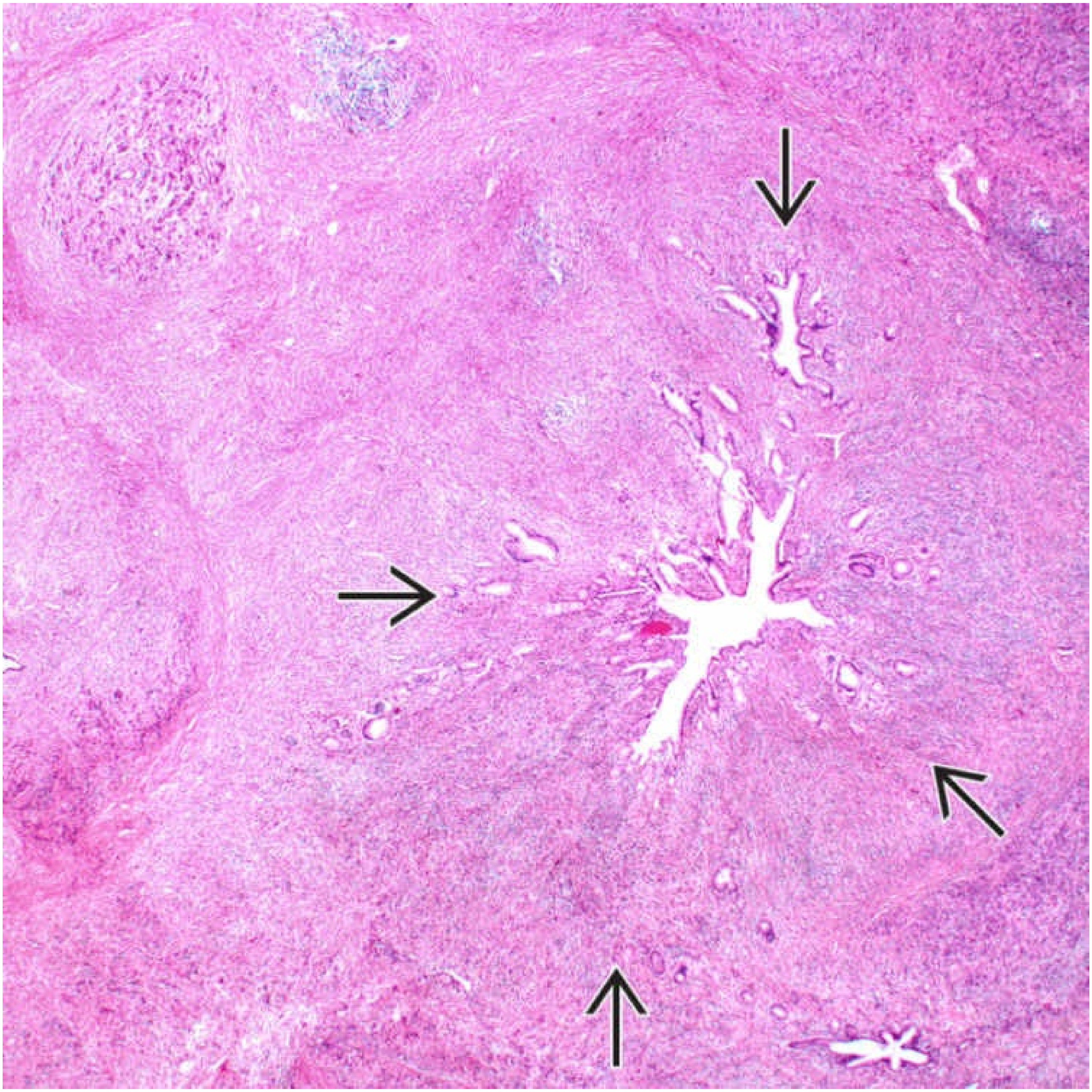
Macroscopic

- Enlarged, firm pancreas ± mass lesion; may mimic adenocarcinoma
  - Usually head is most prominently involved
- Stenosis of pancreatic duct and intrapancreatic common bile duct are common

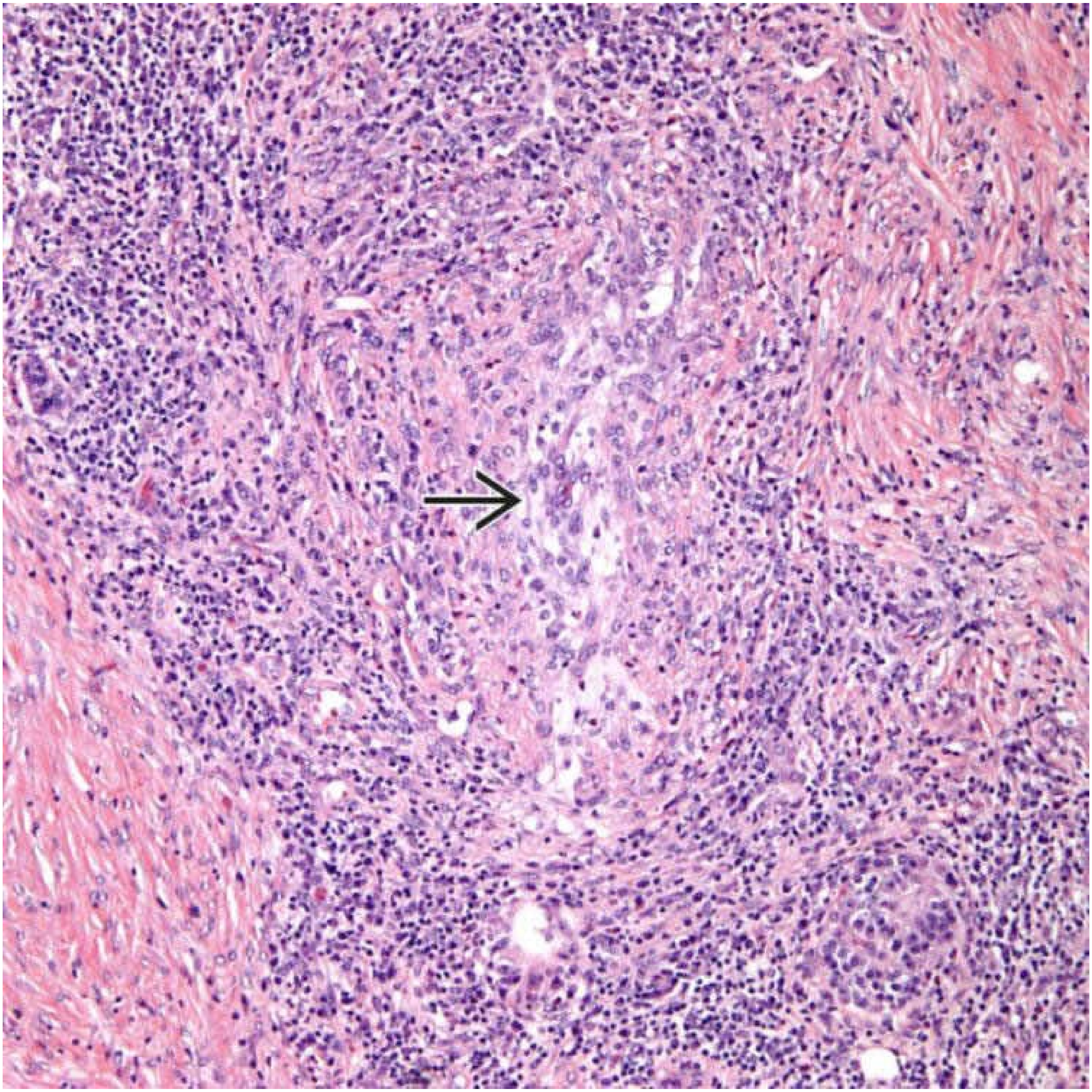
Microscopic

- Dense, lymphoplasmacytic infiltration centered around main and interlobular pancreatic ducts
  - Periductal, lobular, and perilobular fibrosis
  - Obliterative phlebitis and venulitis
  - 2 main types
  - Type 1: Lobular and interlobular distribution, obliterative phlebitis, numerous IgG4(+) plasma cells
  - Type 2: Duct-centric distribution, granulocytic epithelial lesions, only rare IgG(+) plasma cells


Surgical Specimen
This pancreatic resection from a case of type 1 autoimmune pancreatitis (AIP) shows a dense, infiltrative, fibrotic process in the head of the pancreas.

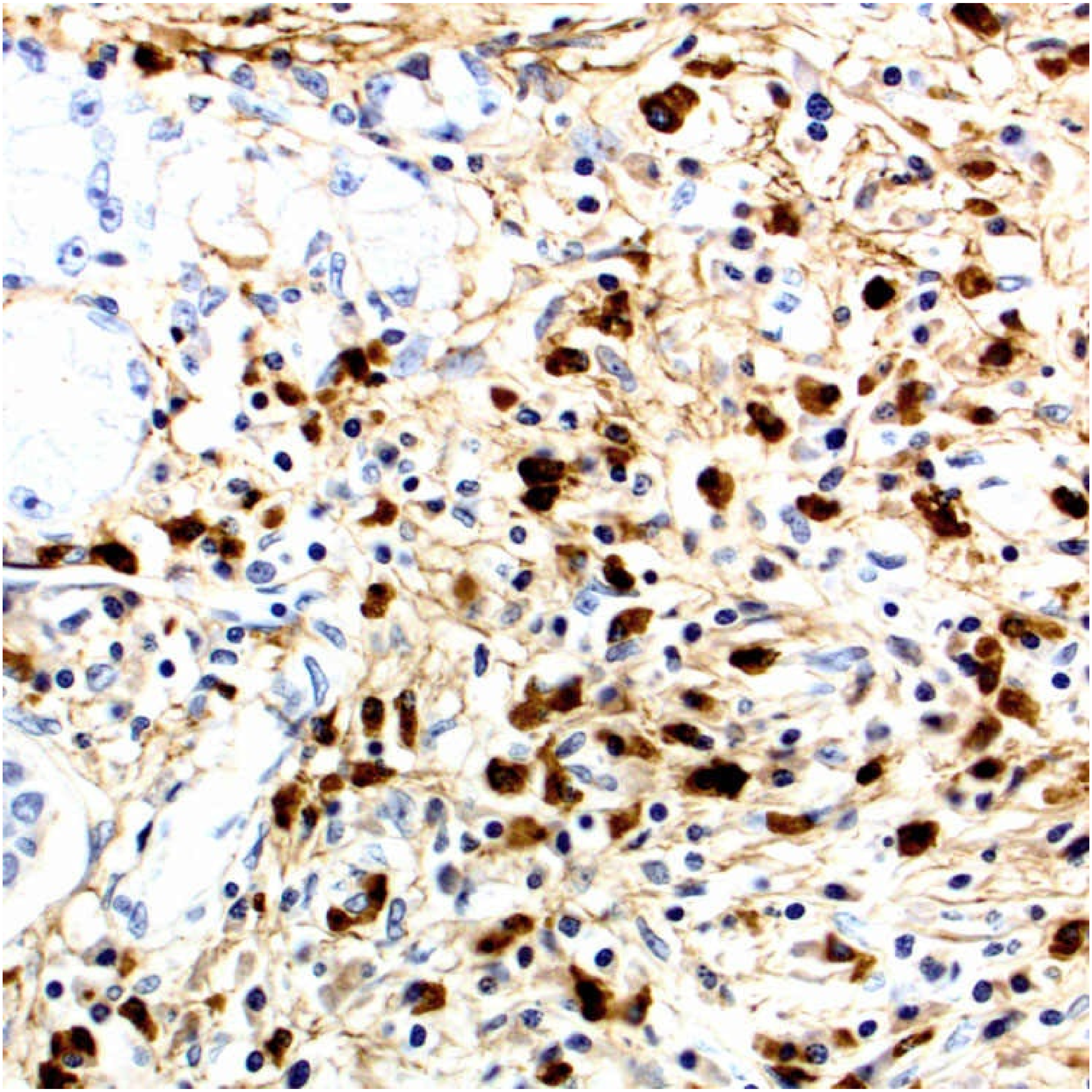


Periductal Inflammation, Type 1 Autoimmune Pancreatitis
Low-power view of type 1 AIP shows marked chronic inflammation surrounding a large duct and involving the periductal stroma → .



Phlebitis, Type 1 Autoimmune Pancreatitis

This vein → has been infiltrated by inflammatory cells, with resultant edema and destruction of the wall of the vessel. Note the surrounding fibrosis.



IgG4 Immunostain, Type 1
IgG4 stain in type 1 AIP shows a large number of IgG4(+) plasma cells (> 10/HPF) in the periductal stroma.

TERMINOLOGY

Abbreviations

- Autoimmune pancreatitis (AIP)

Synonyms

- Lymphoplasmacytic sclerosing pancreatitis (LPSP)

- Idiopathic duct-centric chronic pancreatitis (IDCP)
- Primary sclerosing pancreatitis
- IgG4-related pancreatitis (type 1 only)

Definitions

- Fibroinflammatory disease of presumed autoimmune etiology
  - Other organs can also be affected
- Associated with many other autoimmune diseases
- Specific antigenic trigger unknown

CLINICAL ISSUES

Presentation

- Nonspecific: Jaundice, weight loss, abdominal pain, fatigue

Laboratory Tests

- Elevated serum IgG4 (not invariably present, and not diagnostic of autoimmune pancreatitis)
  - More common in type 1 than type 2 AIP
- Elevated pancreatic enzymes
- ANA often positive

Treatment

- Surgically resected when differentiation from pancreatic cancer is difficult or impossible
- Steroids are very effective treatment

Prognosis

- Steroid therapy is usually very effective
  - Natural regression seen in some cases
  - Recurrence reported in 6-26%

IMAGING

General Features

- Diffusely or segmentally enlarged gland with delayed enhancement
- Segmental or diffuse, irregular duct with narrowing

MACROSCOPIC

General Features

- Markedly firm, enlarged pancreas
  - Usually head is most prominently involved
- Discrete mass lesion variably present
- Stenosis of pancreatic duct and intrapancreatic common bile duct are common

MICROSCOPIC

Histologic Features

- Dense, lymphoplasmacytic infiltration centered around main and interlobular pancreatic ducts
  - Smaller ducts more involved in advanced disease
- Infiltrate may compress lumen and cause infolding of epithelium
- Ductal epithelium may be detached &/or destroyed
- 2 main histologic types
  - **Type 1 AIP**
    - Marked lobular **and** interlobular fibroinflammatory process
    - Plasma cells and eosinophil infiltrates
    - Venulitis and obliterative phlebitis
    - Lymphoid aggregates with variably present germinal centers
    - Often extends into peripancreatic tissue
    - Numerous IgG4(+) plasma cells (on average > 10/HPF)
  - **Type 2 AIP (IDCP)**
    - Fibroinflammatory process with duct-centric distribution
    - Minimal intralobular fibroblastic proliferation
    - Granulocytic epithelial lesions are frequent, consisting of neutrophilic exocytosis, microabscesses, and ductular destruction with reactive epithelial changes
    - Only rare IgG4(+) plasma cells
- Ampulla or bile duct biopsy can be diagnostically helpful

DIFFERENTIAL DIAGNOSIS

Pancreatic Adenocarcinoma

- AIP can mimic adenocarcinoma grossly and radiographically
- Histologically distinct

Inflammatory Myofibroblastic Tumor

- ALK1(+); serum IgG4 not elevated

Alcohol-Related Chronic Pancreatitis

- Diffuse and intralobular fibrosis; not duct-centric; granulocytes rare
- Serum IgG4 not elevated

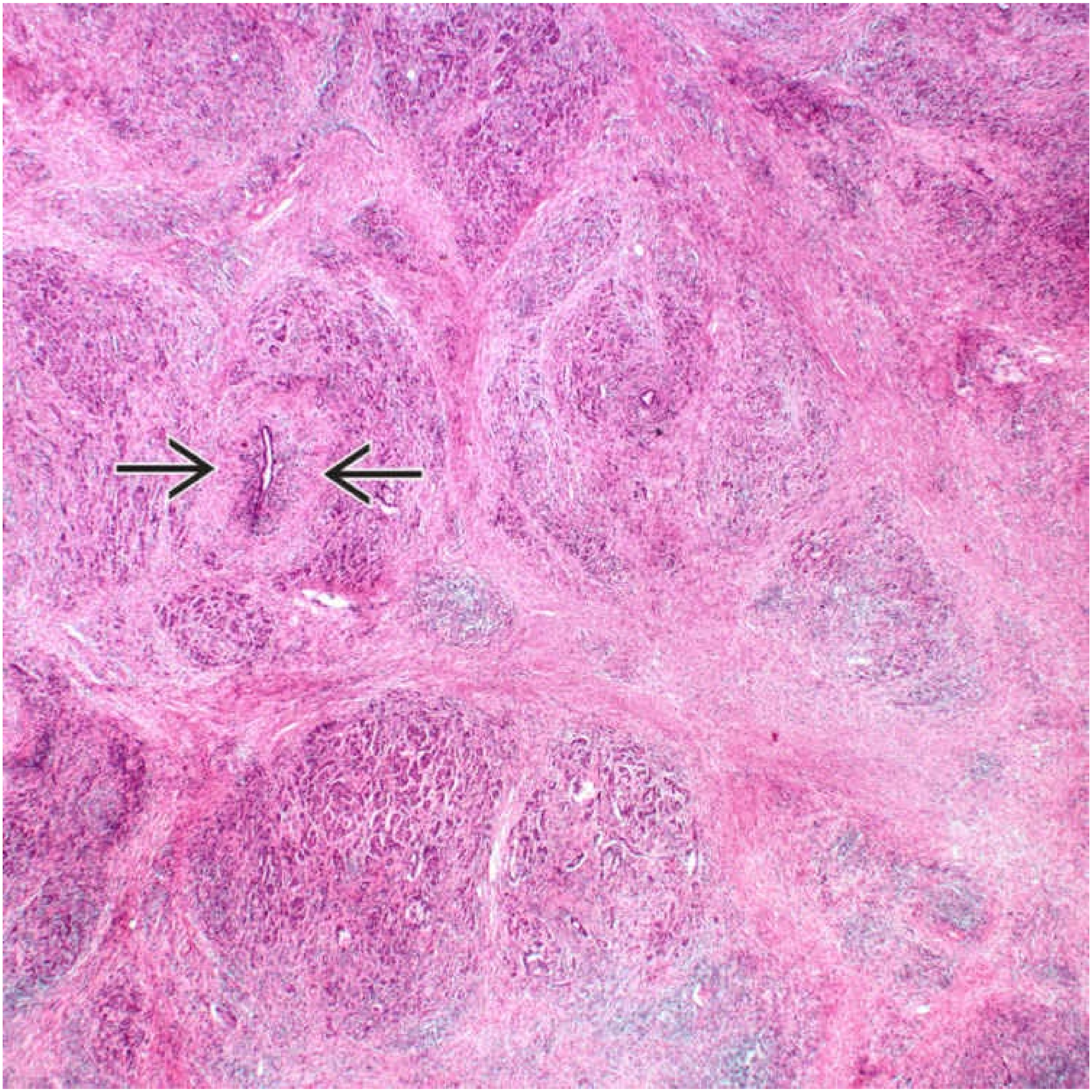
Chronic Obstructive Pancreatitis

- Periductal fibrosis rare; no granulocytes
- Serum IgG4 not elevated

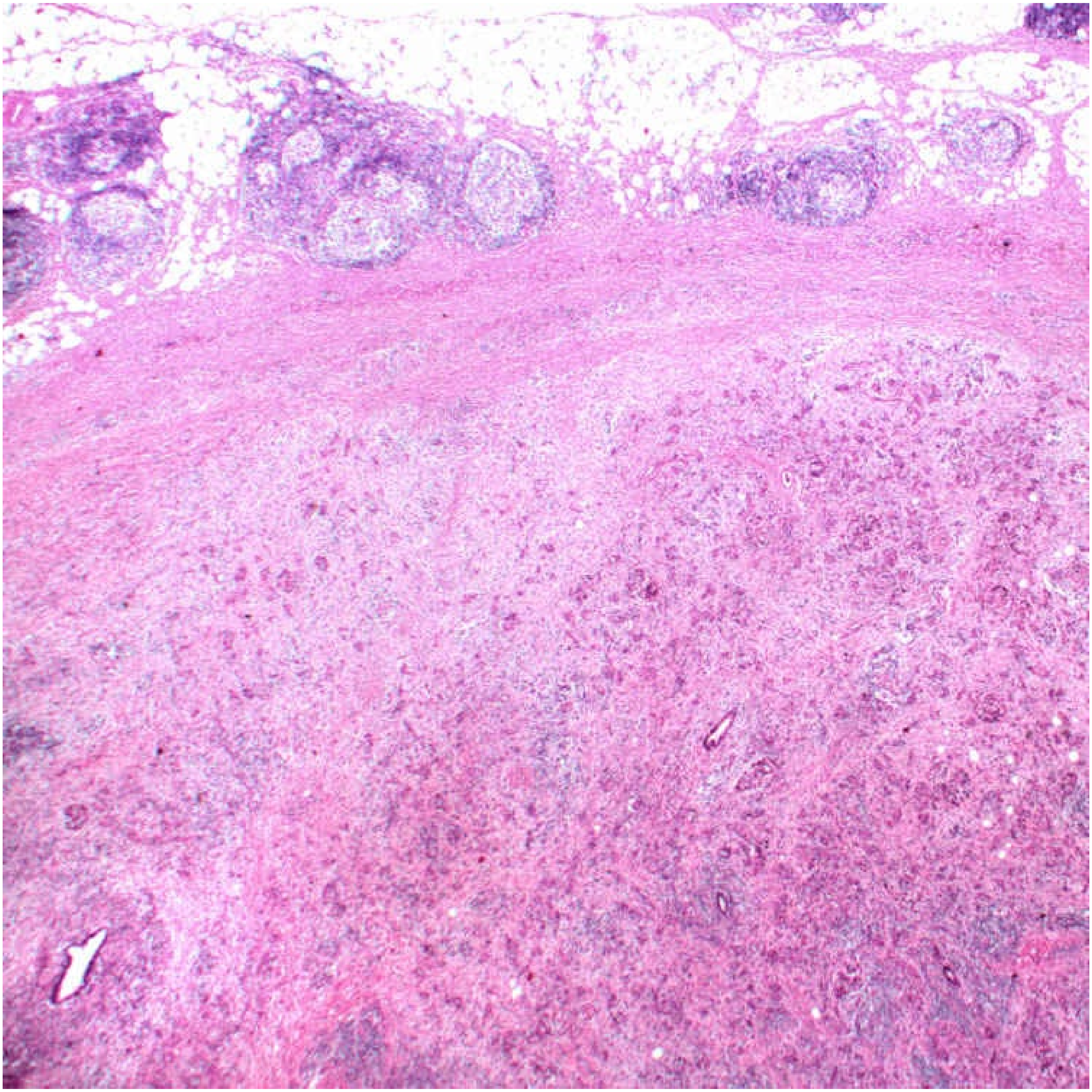
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

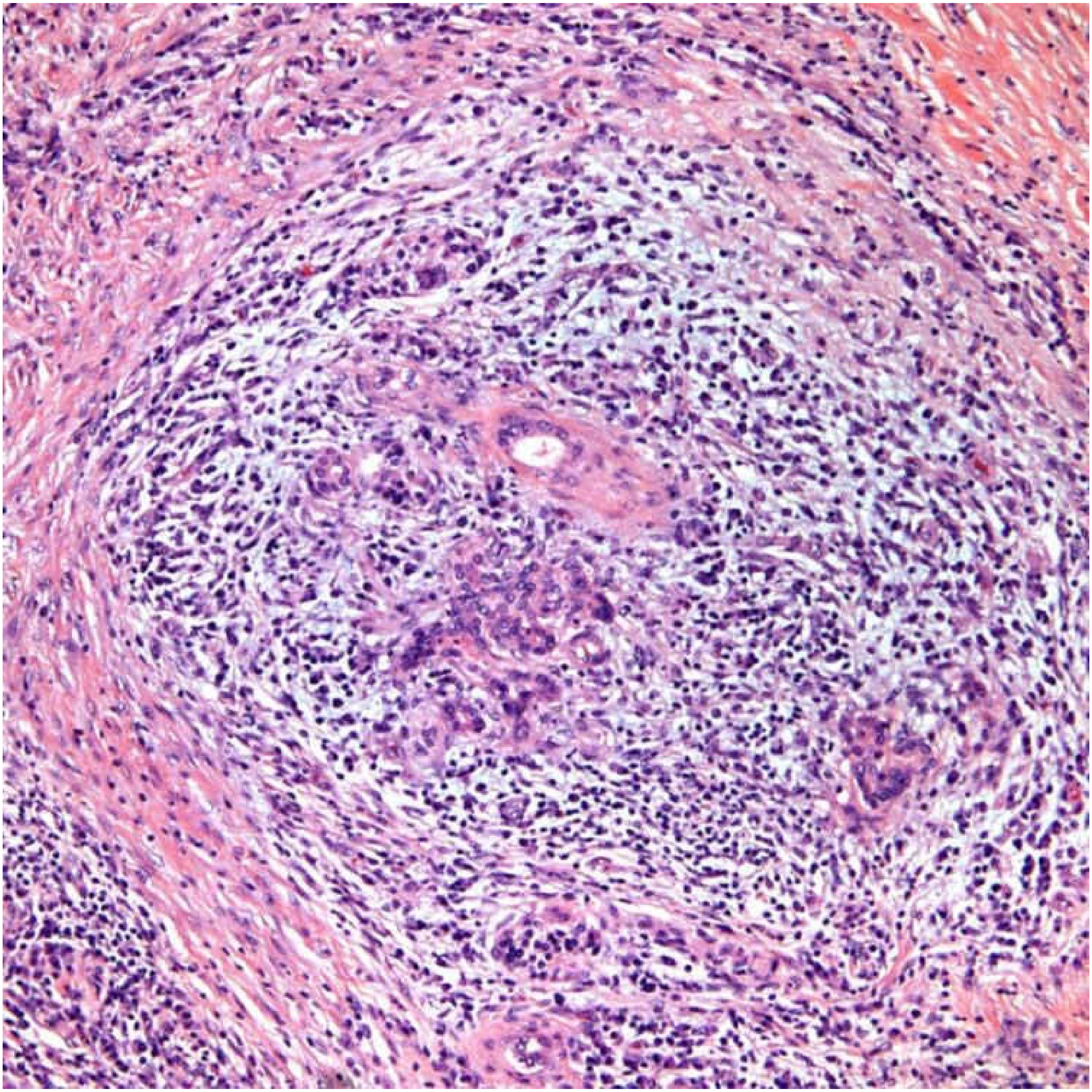
- Often mimics pancreatic adenocarcinoma clinically and radiographically
- Associated with IgG4



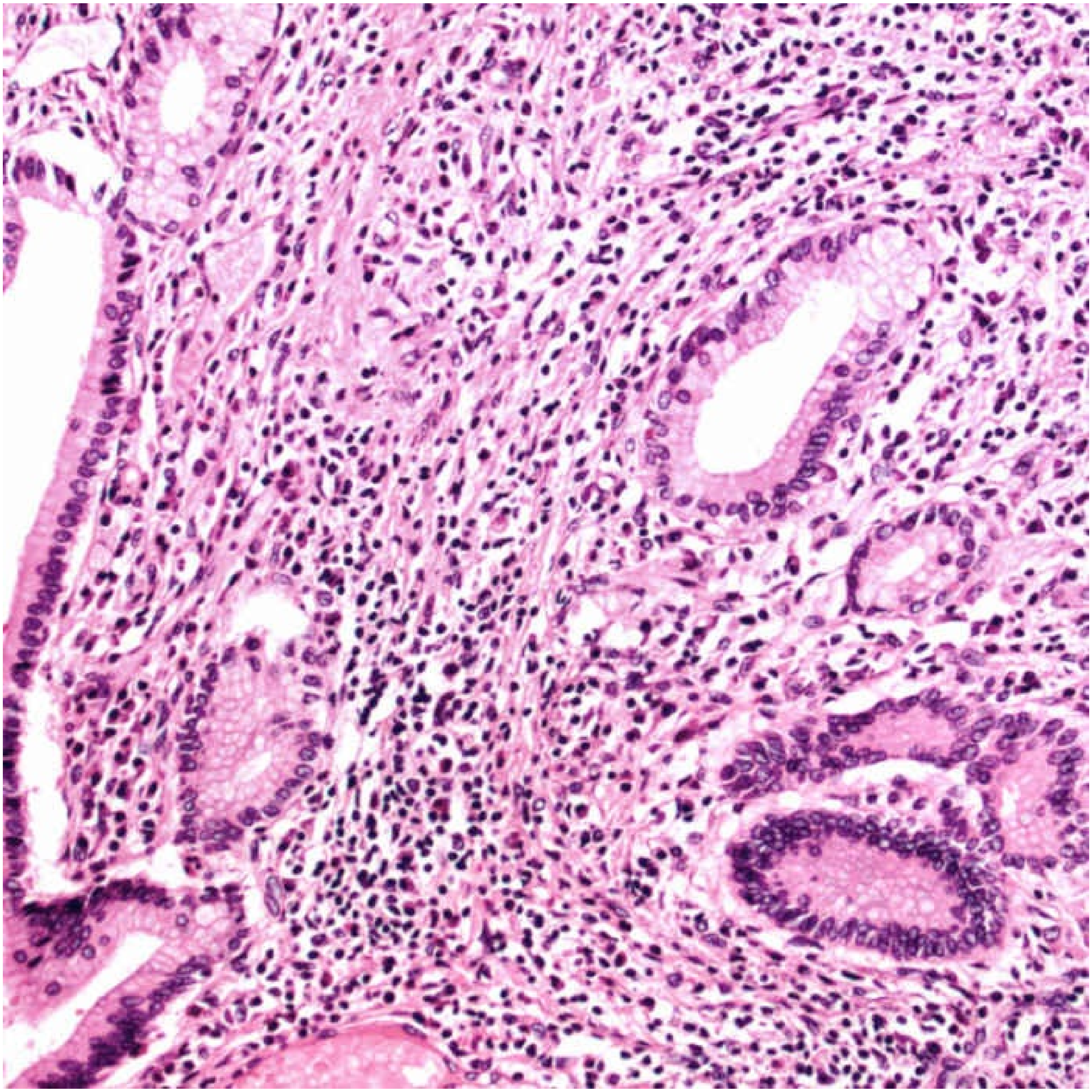
Periductal Fibrosis, Type 1 Autoimmune Pancreatitis
This section of AIP shows a prominent fibroinflammatory process with a periductal accentuation →. This fibrosis and inflammation are both lobular and interlobular.



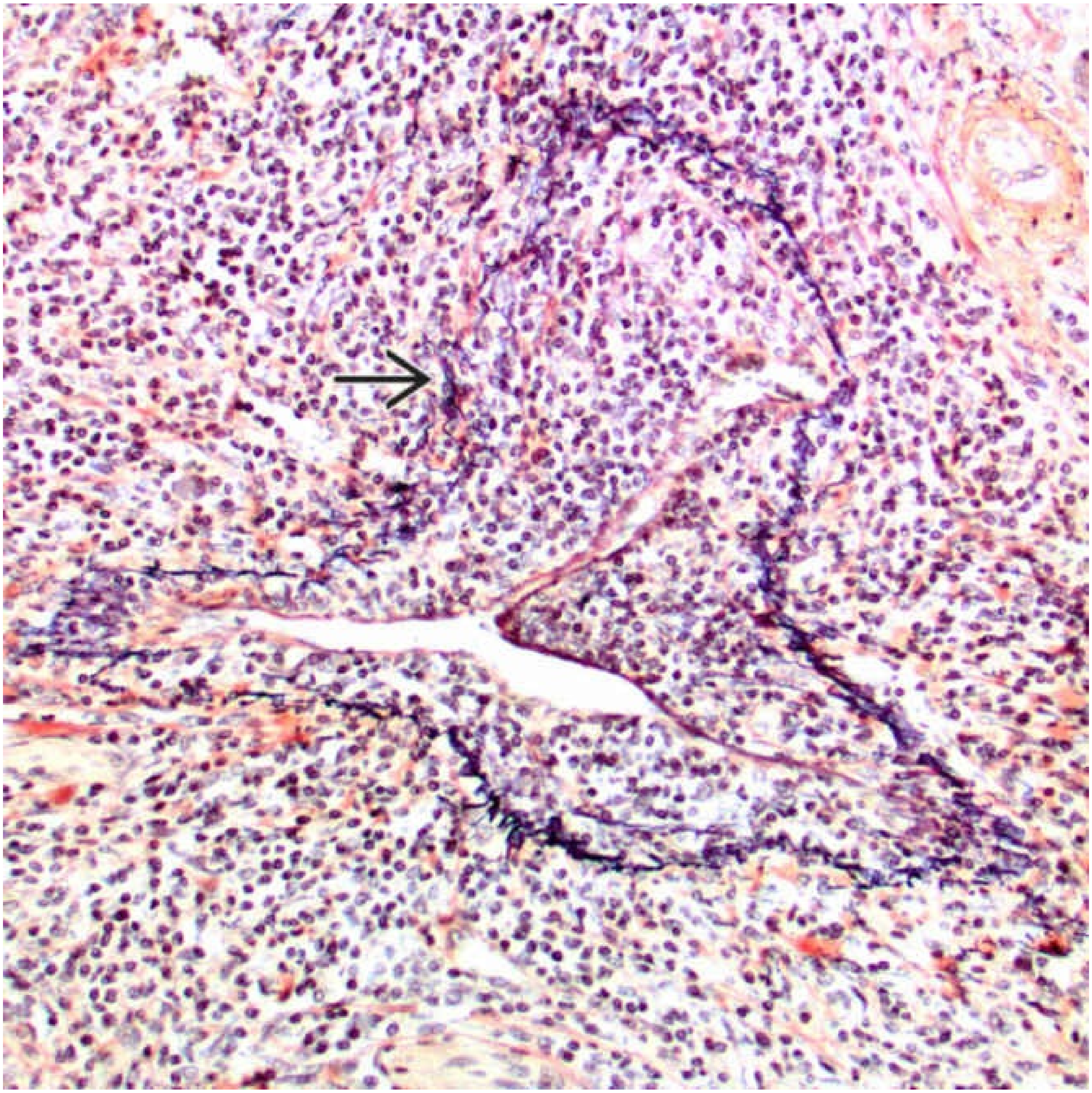
Architectural Effacement, Type 1 Autoimmune Pancreatitis
In type 1 AIP, the fibroinflammatory process extends into the peripancreatic soft tissue with lymphoid follicle formation. Note that the fibroinflammatory process is both lobular and interlobular, effacing the normal pancreatic architecture.



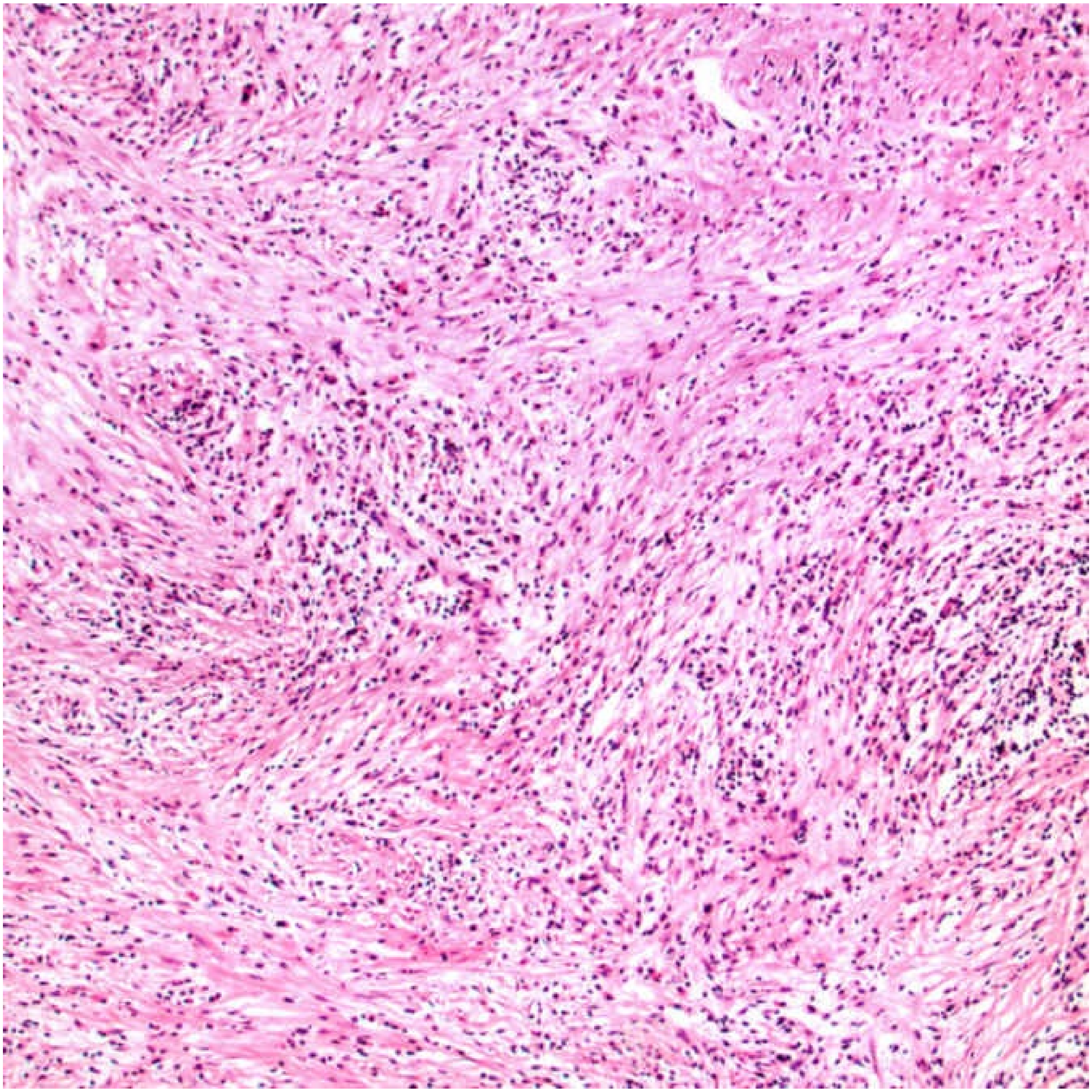
Lobular Destruction, Type 1 Autoimmune Pancreatitis
This pancreatic lobule has been infiltrated by inflammatory cells, and most of the parenchyma destroyed. Only a few small ducts and a small vessel remain.



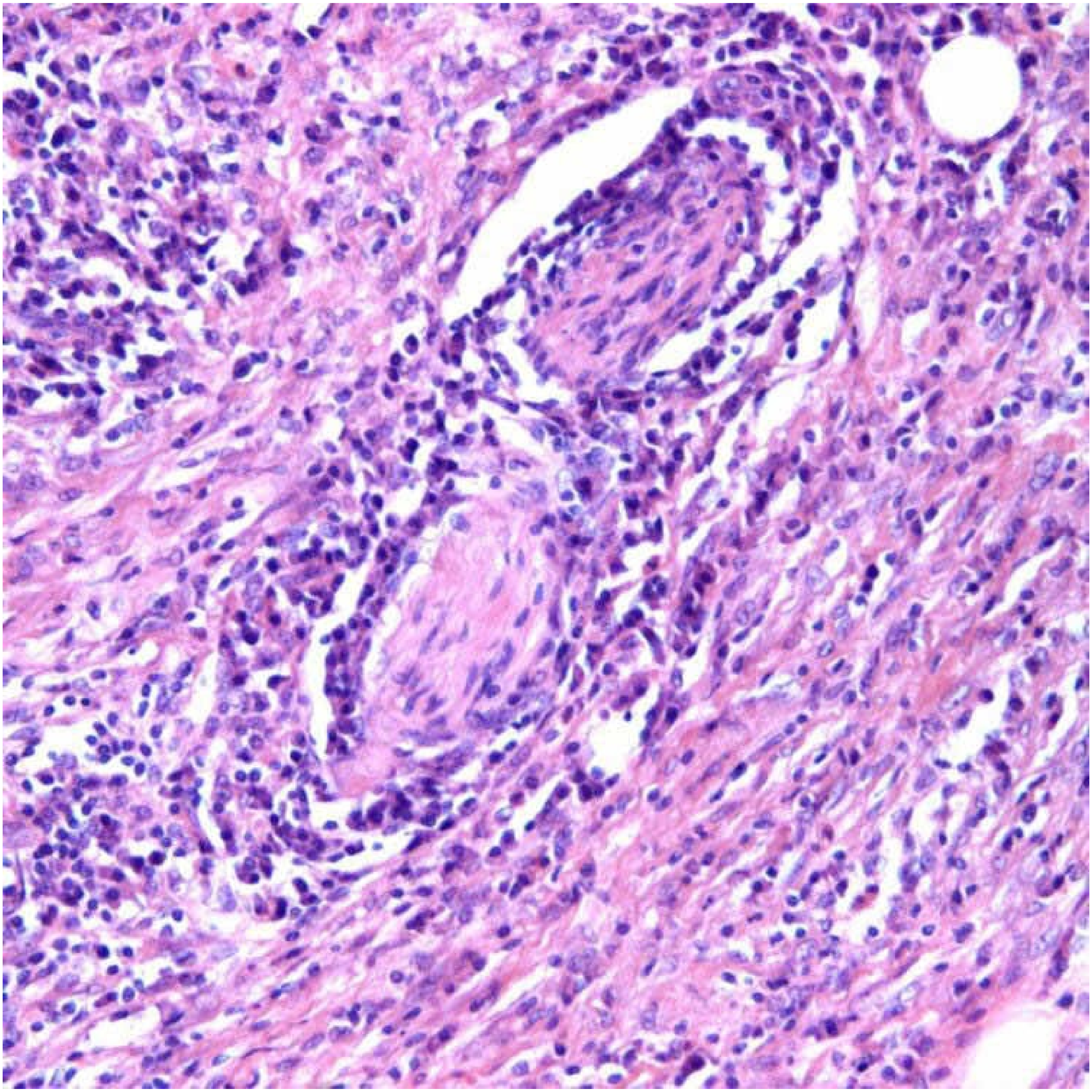
Lymphoplasmacytic Inflammation
The inflammatory infiltrate in AIP typically consists of lymphocytes, numerous plasma cells, and eosinophils.



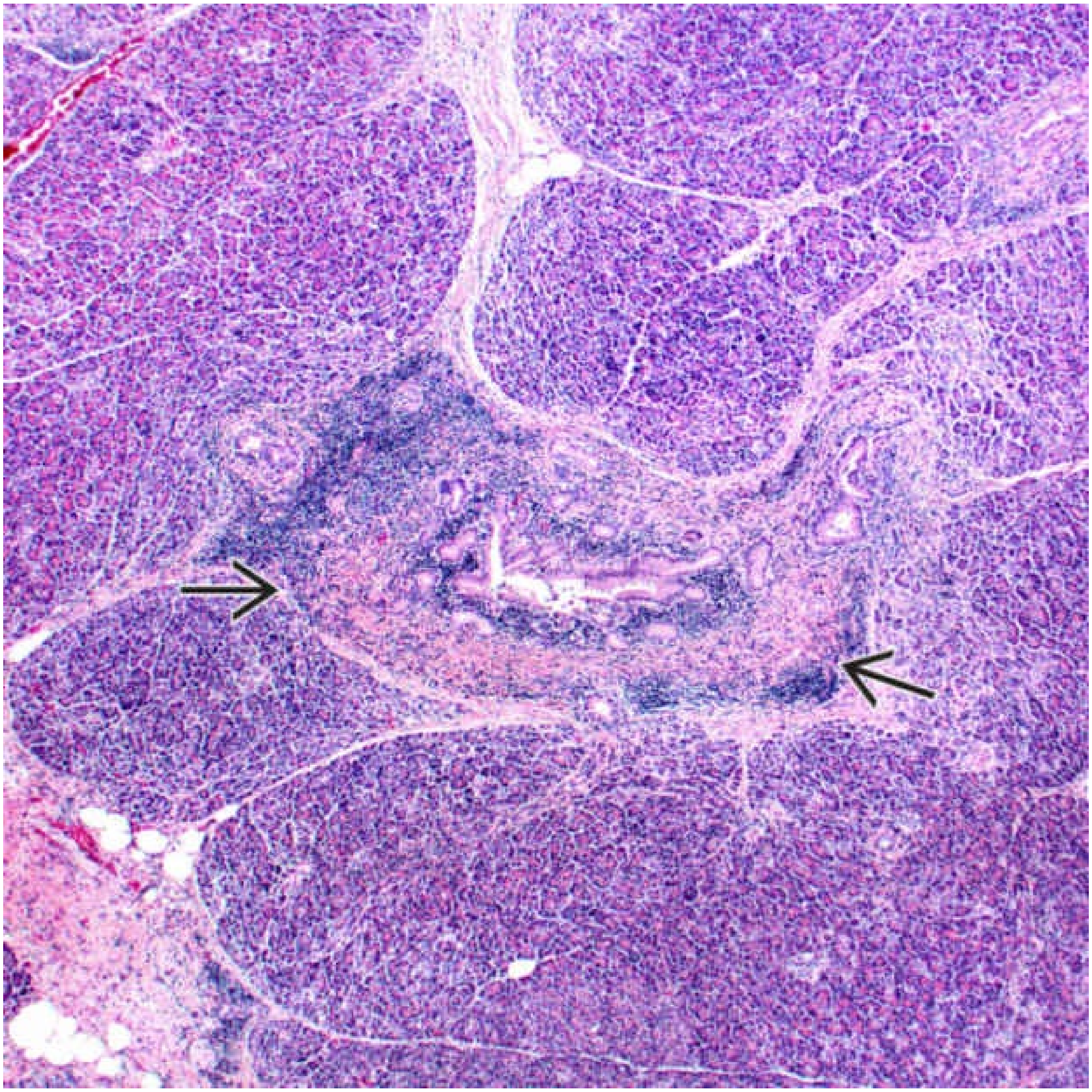
Obliterative Phlebitis, Elastin Stain
An elastic stain highlights the wall of a vein → in a case of type 1 AIP, confirming the presence of obliterative phlebitis.



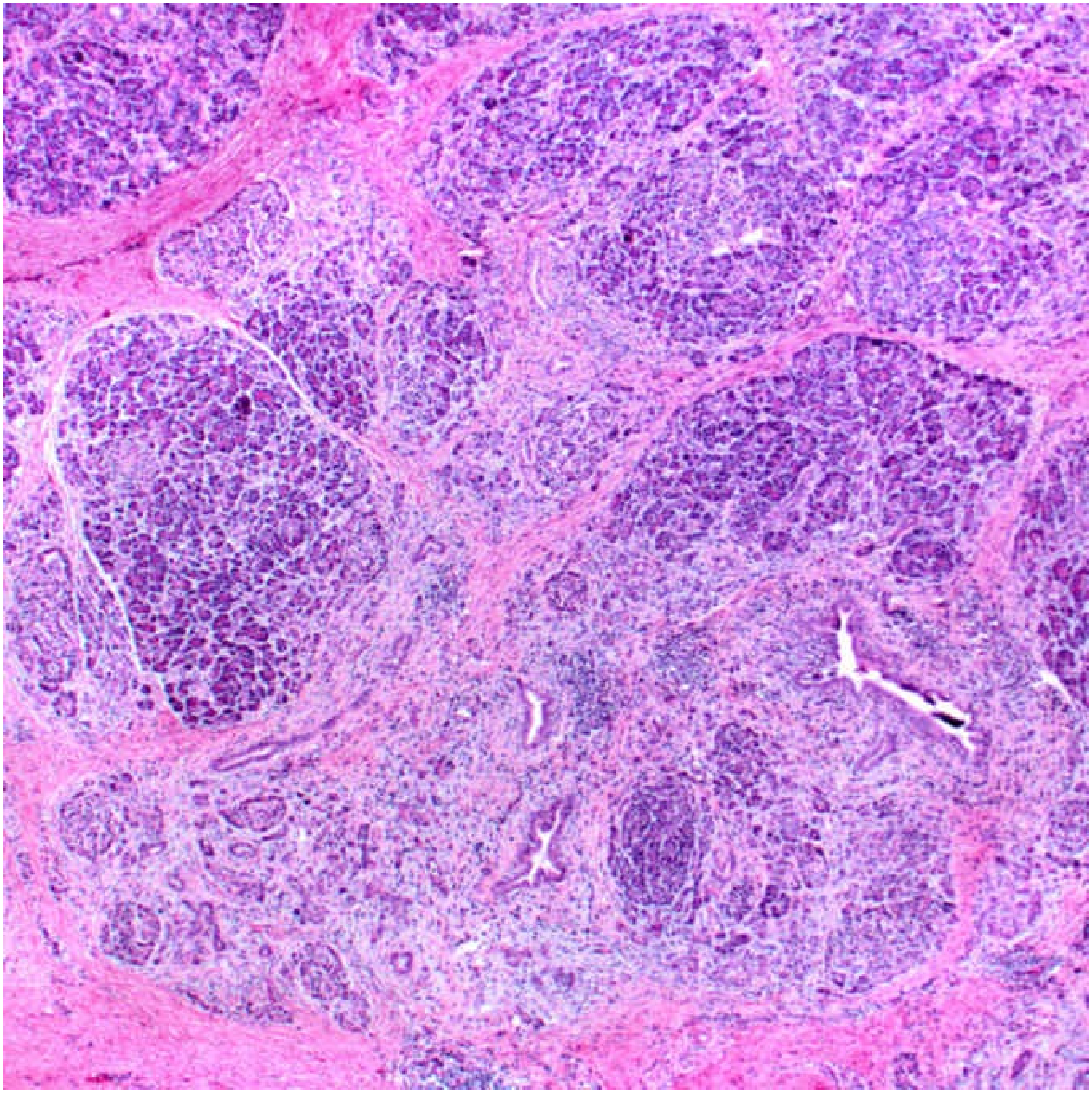
Interlobular Fibrosis
In AIP, the normal interlobular stroma may be replaced by a storiform pattern of fibrosis with a mixture of chronic inflammatory cells including eosinophils.



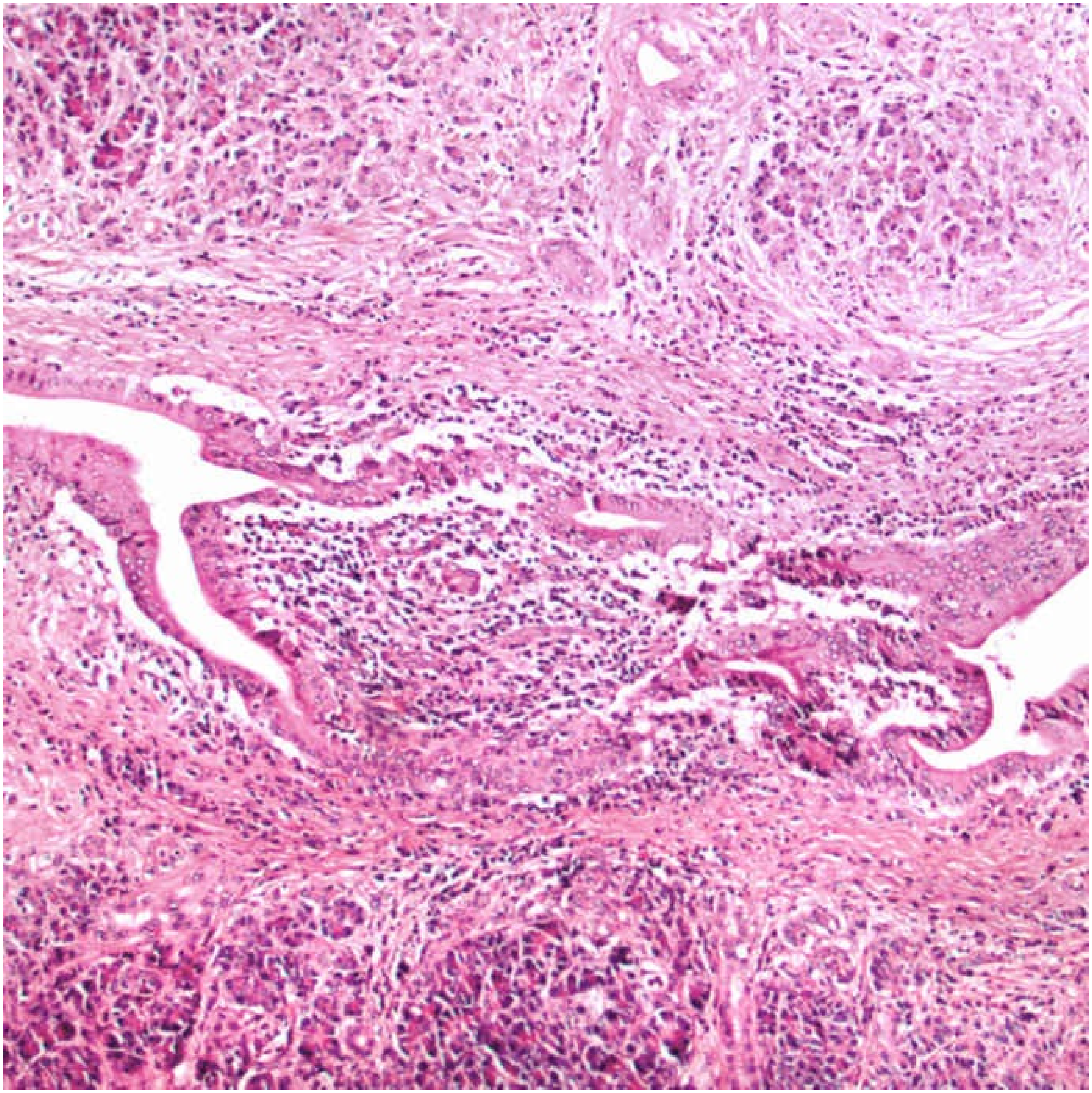
Perineural Inflammation
Perineural inflammation is common in AIP. Note the dense infiltrate of plasma cells surrounding this nerve.



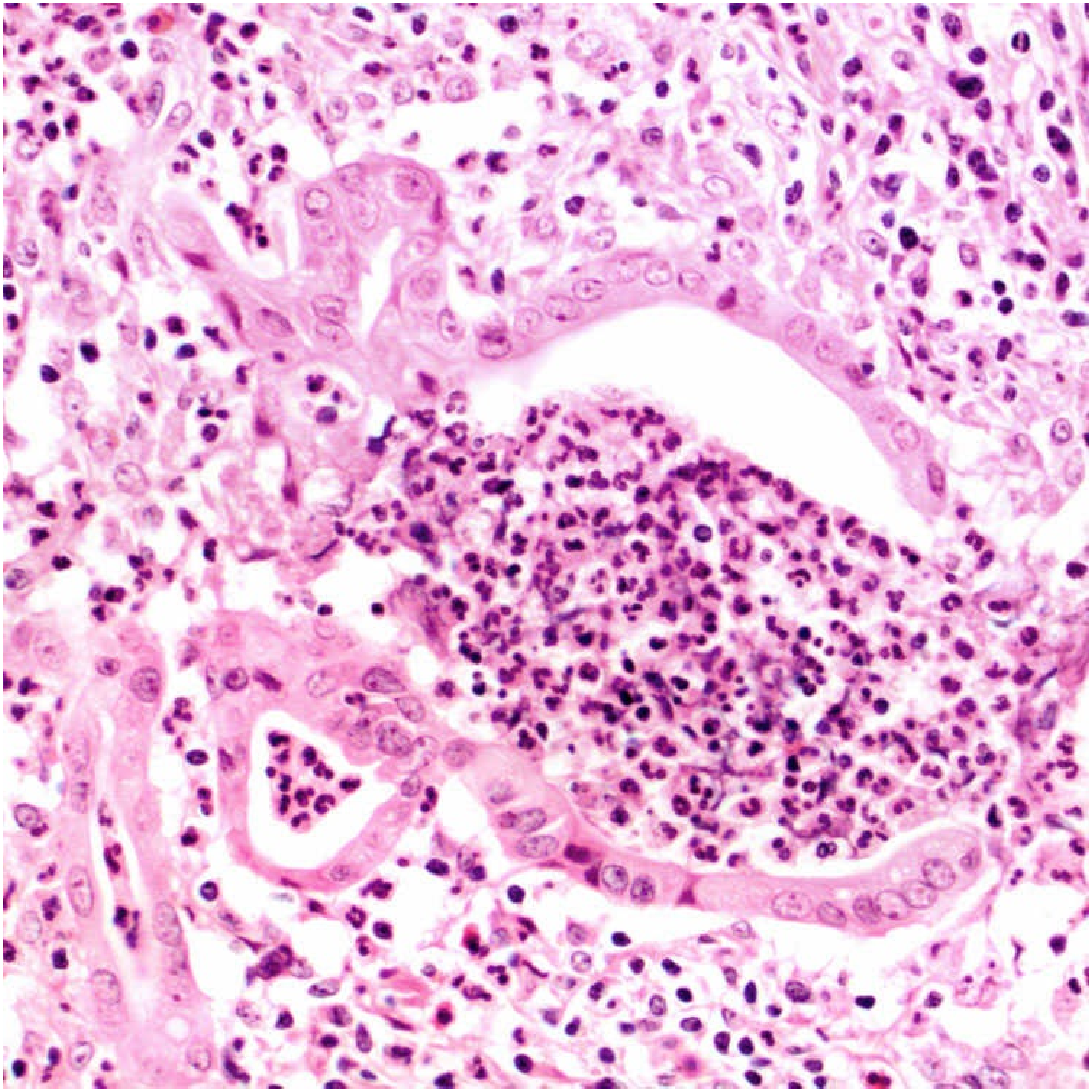
Type 2 Autoimmune Pancreatitis, Low Power
In type 2 AIP, the fibroinflammatory process is limited to the periductal region → without significant lobular destruction or interlobular fibrosis.



Type 2 Autoimmune Pancreatitis, Low Power
In comparison with type 1 AIP, destruction of lobules is less prominent in this example of idiopathic duct-centric chronic pancreatitis. Marked edema may be seen within lobules &/or the perilobular interstitium.

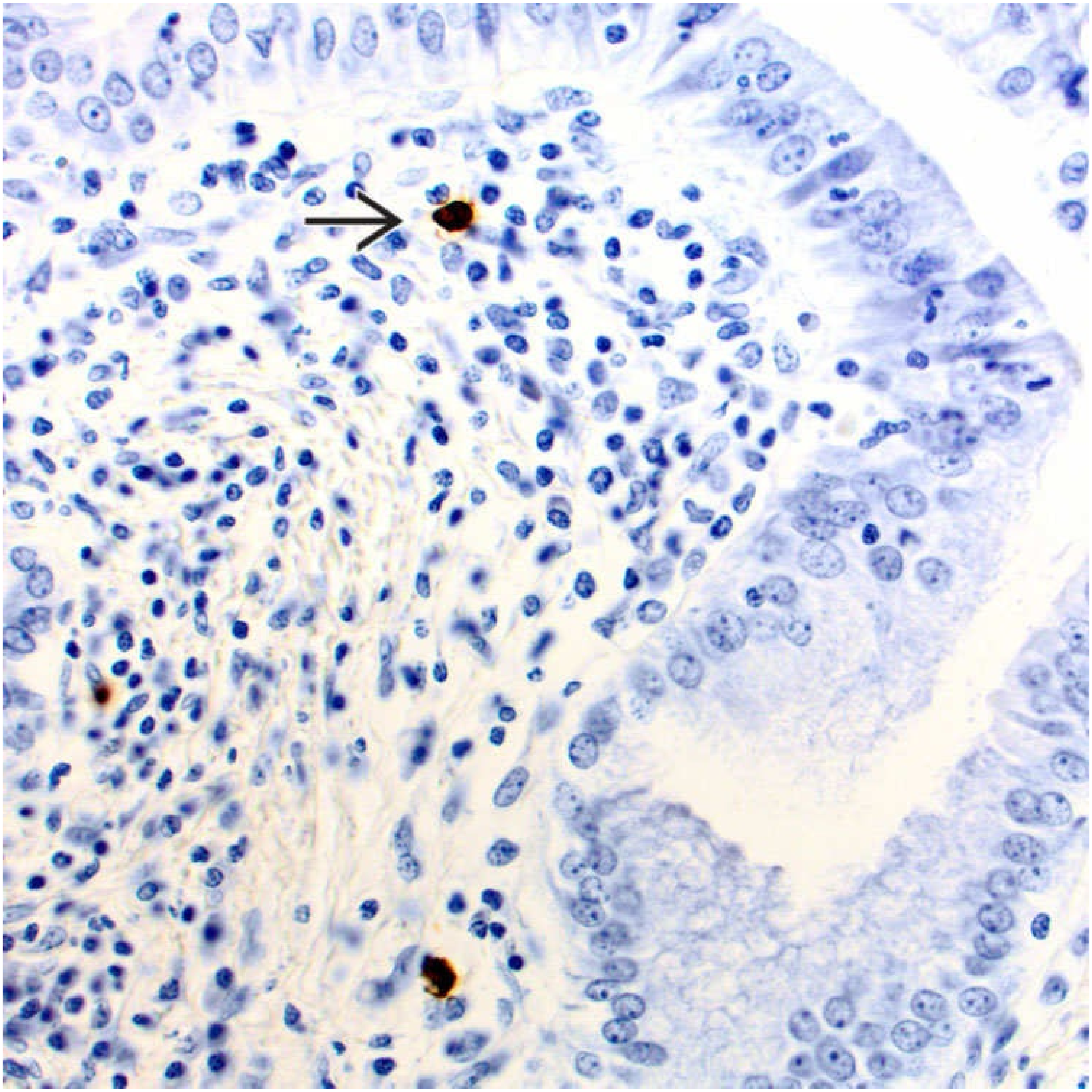


Type 2 Autoimmune Pancreatitis, Duct Stenosis
An interlobular duct is distorted and stenotic due to marked inflammation (with numerous neutrophils) and reactive epithelial changes in type 2 AIP.



Granulocytic Epithelial Lesion

Granulocytic epithelial lesions are typical of type 2 AIP. Features include numerous neutrophils infiltrating duct epithelium and filling duct lumina, with destruction of epithelium and reactive epithelial atypia.



Type 2 Autoimmune Pancreatitis, IgG4 Stain
IgG4 stain in type 2 AIP shows that IgG4(+) plasma cells → are rare.

SELECTED REFERENCES

1. Madhani, K, et al. Autoimmune Pancreatitis: An Update on Diagnosis and Management. *Gastroenterol Clin North Am*. 2016; 45(1):29–43.
2. Hart, PA, et al. Recent Advances in Autoimmune Pancreatitis. *Gastroenterology*. 2015; 149(1):39–51.
4. Sepehr, A, et al. IgG4+ to IgG+ plasma cells ratio of ampulla can help differentiate autoimmune pancreatitis from other "mass forming" pancreatic lesions. *Am J Surg Pathol*. 2008; 32(12):1770–1779.
5. Deshpande, V, et al. Autoimmune pancreatitis: a systemic immune complex mediated disease. *Am*

J Surg Pathol. 2006 Dec; 30(12):1537–1545. [Erratum in: Am J Surg Pathol. 31(2):328, 2007].
6. Chari, ST, et al. Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. *Clin Gastroenterol Hepatol*. 2006; 4(8):1010–1016. [quiz 934].
7. Finkelberg, DL, et al. Autoimmune pancreatitis. *N Engl J Med*. 2006; 355(25):2670–2676.
8. Deshpande, V, et al. Autoimmune pancreatitis: more than just a pancreatic disease? A contemporary review of its pathology. *Arch Pathol Lab Med*. 2005; 129(9):1148–1154.
9. Mino-Kenudson, M, et al. Histopathology of autoimmune pancreatitis: recognized features and unsolved issues. *J Gastrointest Surg*. 2005; 9(1):6–10.
11. Notohara, K, et al. Idiopathic chronic pancreatitis with periductal lymphoplasmacytic infiltration: clinicopathologic features of 35 cases. *Am J Surg Pathol*. 2003; 27(8):1119–1127.

3. Kamisawa, T, et al. Recent advances in autoimmune pancreatitis: type 1 and type 2. *Gut*. 2013; 62(9):1373–1380.
10. Zamboni, G, et al. Histopathological features of diagnostic and clinical relevance in autoimmune pancreatitis: a study on 53 resection specimens and 9 biopsy specimens. *Virchows Arch*. 2004; 445(6):552–563.

Groove Pancreatitis

KEY FACTS

Terminology

- Distinct form of pancreatitis that results in fibrosis of paraduodenal region in vicinity of minor ampulla
- Significant because dense fibrosis and irregular borders can mimic neoplasm

Etiology/Pathogenesis

- Disease develops in individuals with anomalies of minor ampulla, conceivably leading to outflow obstruction, with alcohol as precipitating factor

Clinical Issues

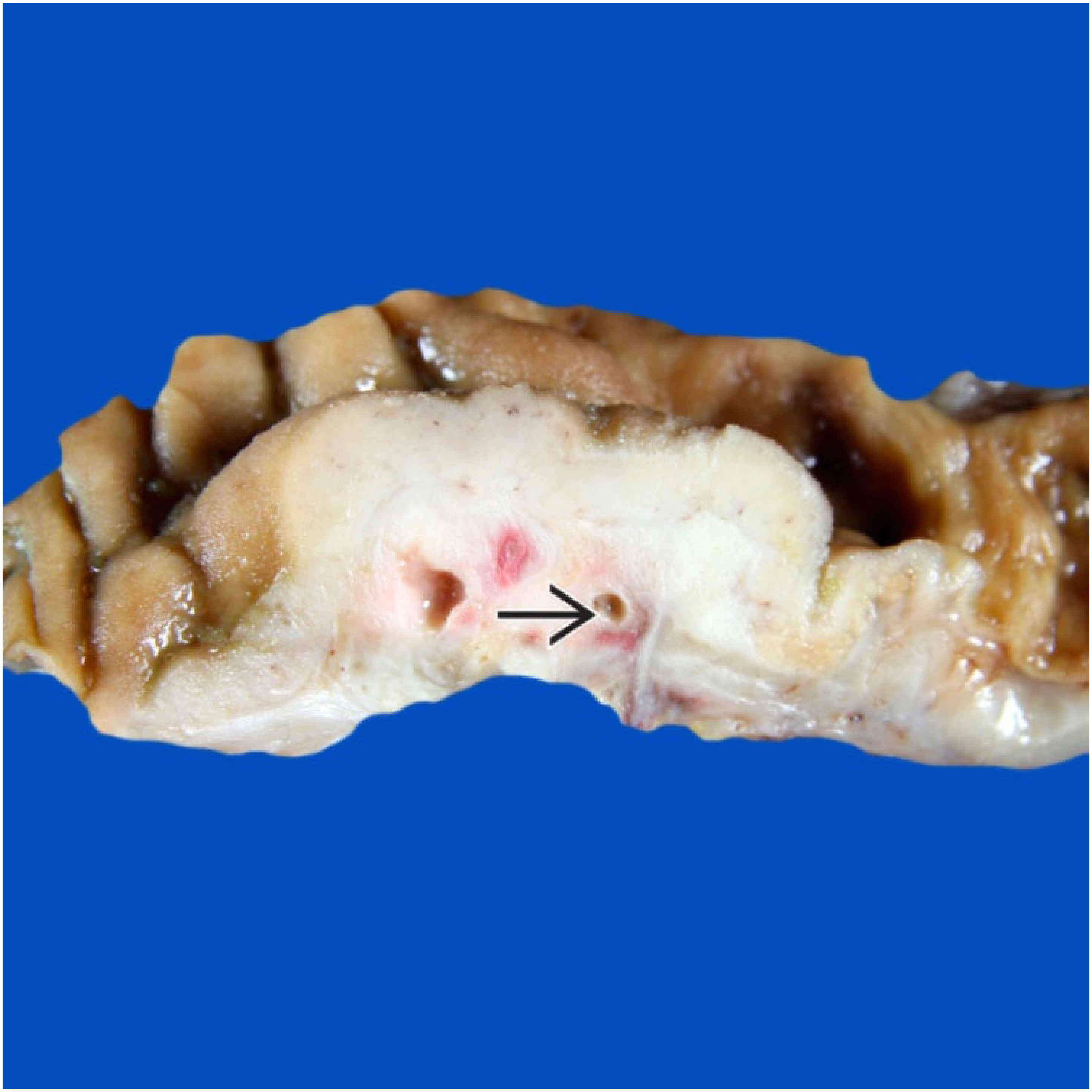
- Typically occurs in men with history of alcohol use
- Symptoms include abdominal pain, vomiting, and weight loss

Macroscopic

- Thickening and fibrosis of duodenum wall and paraduodenal pancreas with cyst formation
  - Changes are centered around minor papilla and involve “groove” between pancreas and duodenum
  - May mimic pancreatic neoplasm, including cystic neoplasm

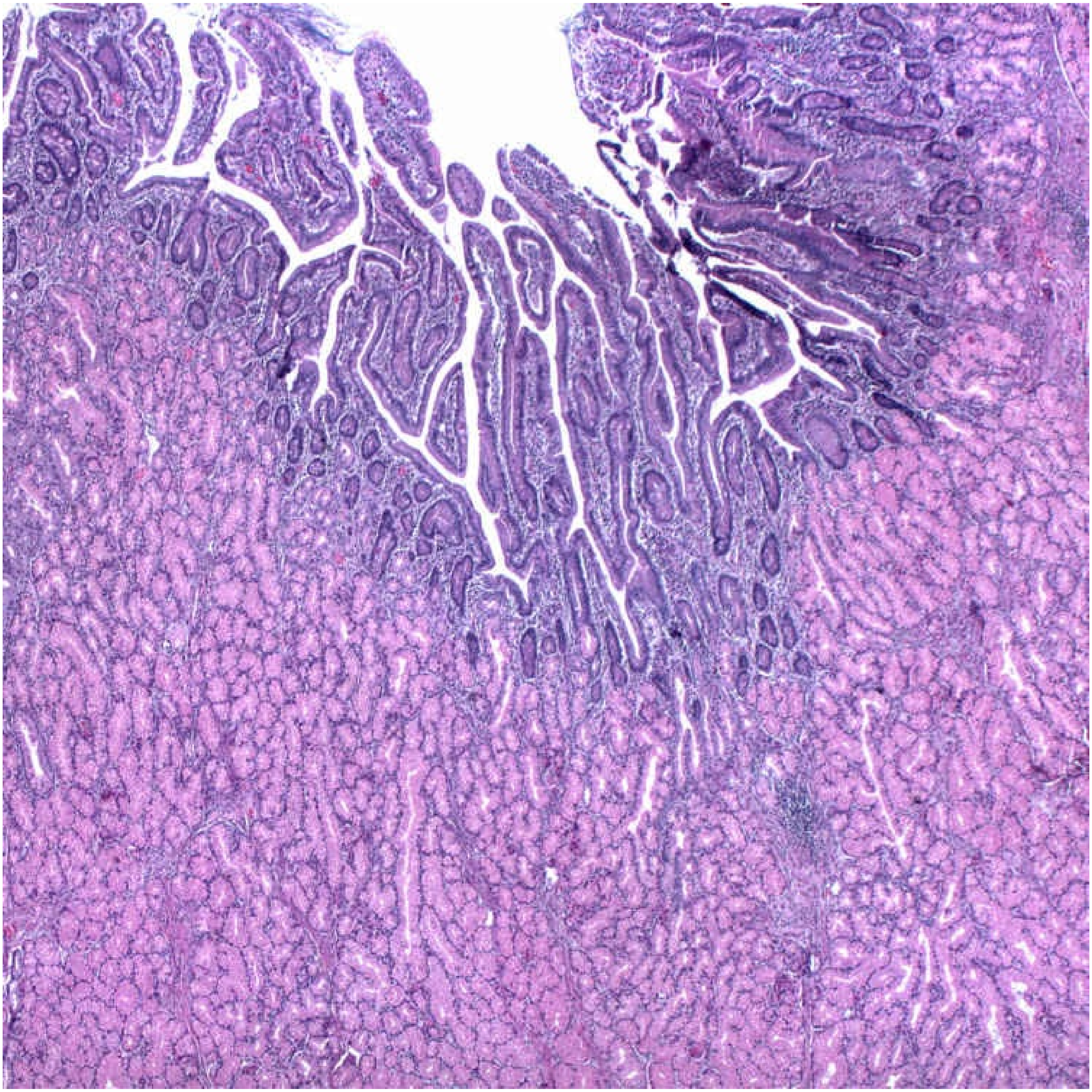
Microscopic

- Duodenal wall around minor ampulla is thickened with marked fibrosis involving muscular propria and adjacent head of pancreas
  - Fibrosis extends into head of pancreas and may involve common bile duct
  - Duodenal fibrosis is frequently accompanied by cysts lined by granulation tissue
- Nonparaduodenal pancreas frequently shows dilated ducts with inspissated secretions and prominent interlobular fibrosis
- Brunner gland hyperplasia is commonly seen

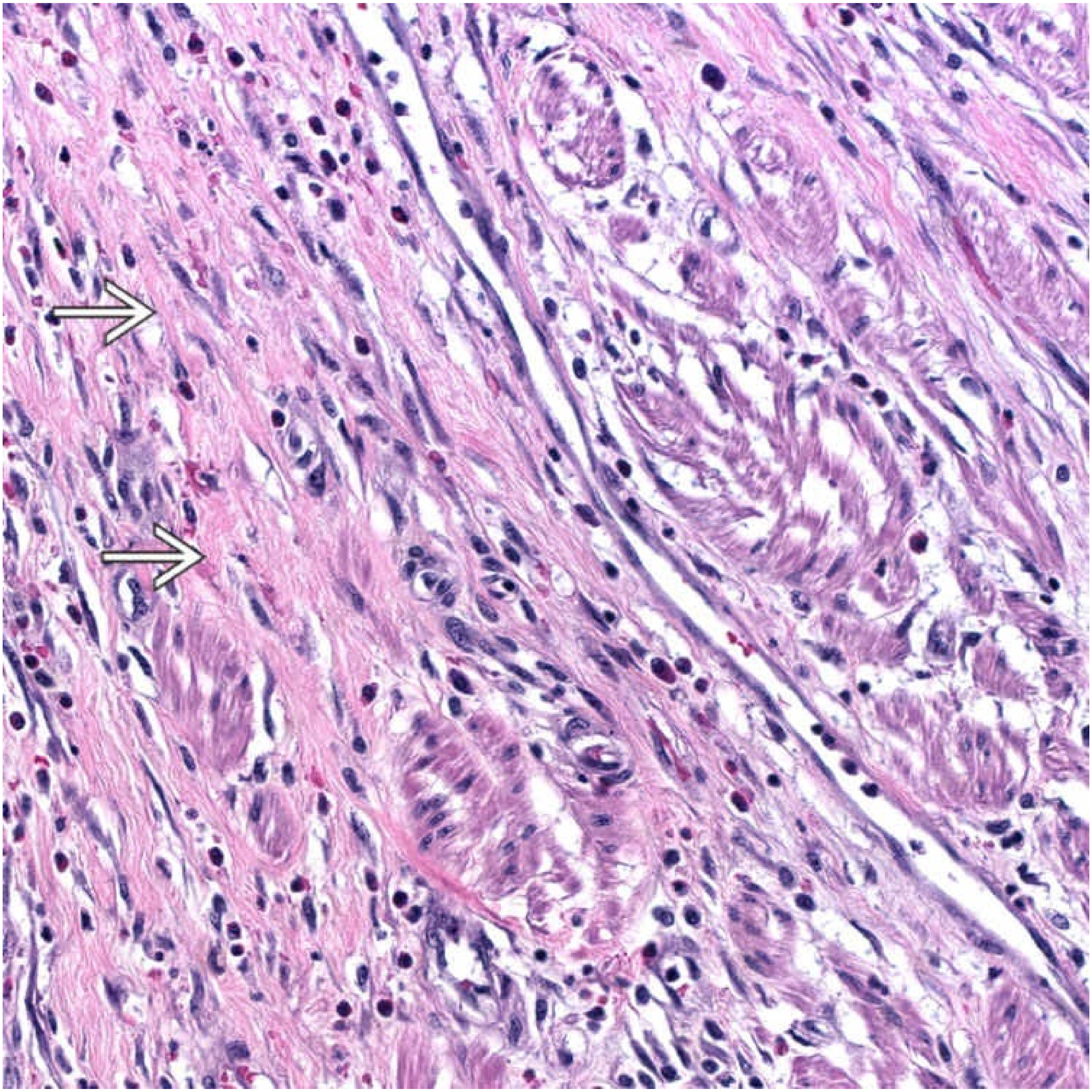


Fibrosis and Cysts

Gross photograph of a pancreaticoduodenectomy specimen shows a mass-like lesion beneath the duodenal mucosa. Note the paraduodenal zone of fibrosis with numerous small cysts →.

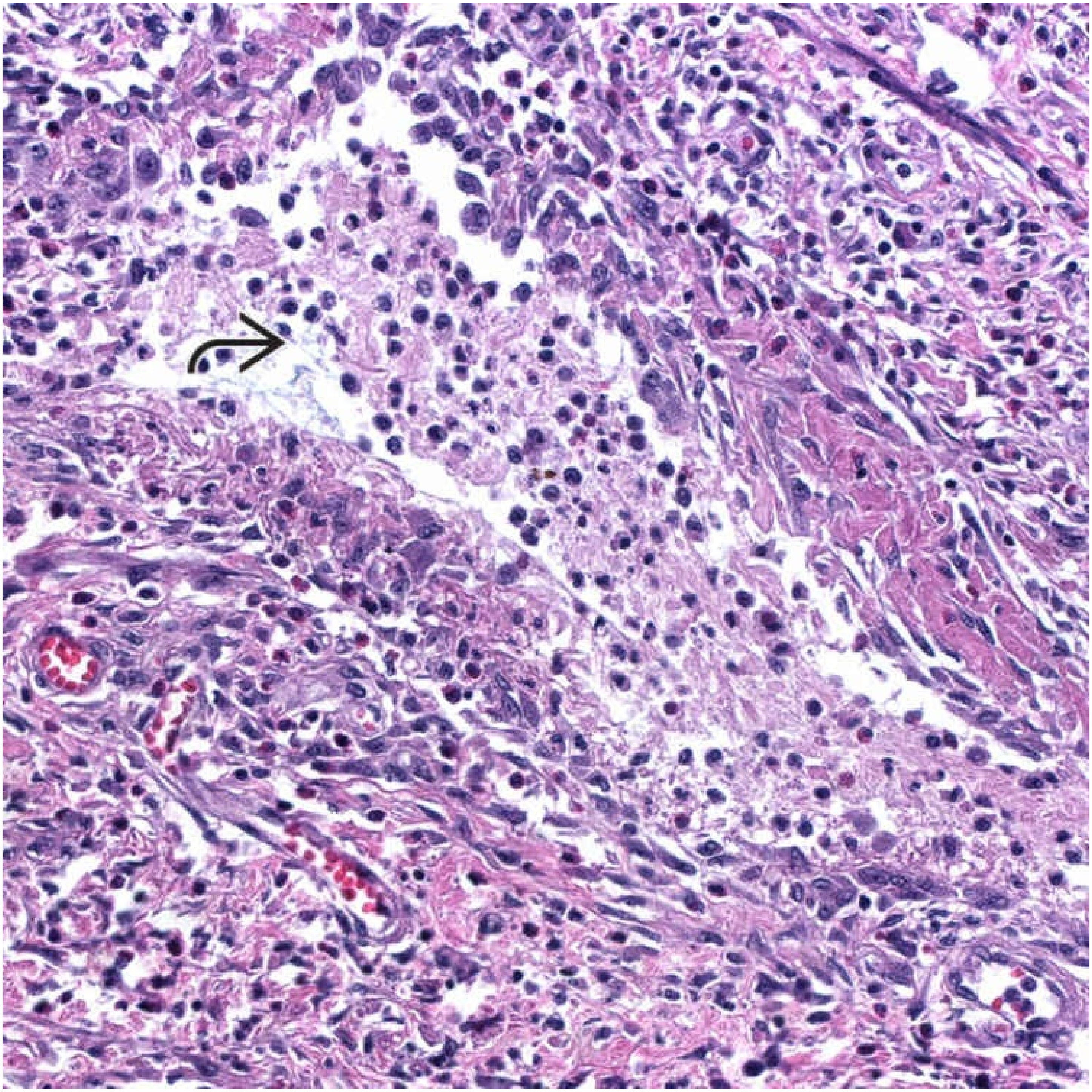


Brunner Gland Hyperplasia
Prominent Brunner gland hyperplasia in the region of the minor ampulla frequently accompanies groove pancreatitis.



Muscularis Propria Fibrosis

High-power view of groove pancreatitis shows exuberant fibrosis ⇒ within the muscularis propria.



Cyst Formation

Cyst formation is frequently seen in groove pancreatitis, accounting for one of the plethora of names used for this entity, “paraduodenal wall cyst.”

TERMINOLOGY

Synonyms

- Paraduodenal pancreatitis
- Cystic dystrophy of heterotopic pancreas
- Paraduodenal wall cyst
- Pancreatic hamartoma of duodenum
- Myoadenomatosis

Definitions

- Distinct form of pancreatitis that results in fibrosis of paraduodenal region in vicinity of minor ampulla
- Significant because dense fibrosis and irregular borders can mimic neoplasm

ETIOLOGY/PATHOGENESIS

Combination of Factors

- Developmental anomalies and environmental exposure
  - Anatomical/functional variations in region of minor papilla, such as pancreatic divisum, predispose to development of groove pancreatitis
- History of alcohol use is common
- Likely that disease develops in individuals with anomalies of minor ampulla, conceivably leading to outflow obstruction, with alcohol as precipitating factor

CLINICAL ISSUES

Epidemiology

- Incidence
  - Uncommon
- Age
  - Middle age
- Sex
  - Predominantly male

Presentation

- Abdominal pain
- Vomiting caused by stenosis of duodenum
- Weight loss
- Jaundice is rare

Treatment

- Whipple resection may be required to exclude malignancy
- Conservative medical treatment in majority of cases

IMAGING

Ultrasonographic Findings

- Hypoechoic area is seen between duodenal wall and pancreatic parenchyma on endoscopic ultrasound
  - Narrowing of duodenal wall &/or common bile duct may be seen

CT Findings

- Hypodense lesion between pancreatic head and duodenum
- Variably present, cyst-like changes in duodenal wall or groove area

MACROSCOPIC

General Features

- Changes are centered around minor papilla and involve “groove” between pancreas and duodenum
- Thickening and fibrosis of duodenum and paraduodenal pancreas may be mistaken for pancreatic carcinoma
- ~ 1/2 of lesions are cystic, and some may mimic pancreatic cystic neoplasm

MICROSCOPIC

Histologic Features

- Duodenal wall around minor papilla is thickened with marked fibrosis involving muscular propria
  - Fibrosis extends into head of pancreas and may involve common bile duct
  - Duodenal fibrosis is frequently accompanied by cyst formation
  - Cysts are lined by inflammatory granulation tissue
- Brunner gland hyperplasia is commonly seen
- Nonparaduodenal pancreas frequently shows dilated ducts with inspissated secretions and prominent interlobular fibrosis

DIFFERENTIAL DIAGNOSIS

Chronic Pancreatitis, Alcohol-Related

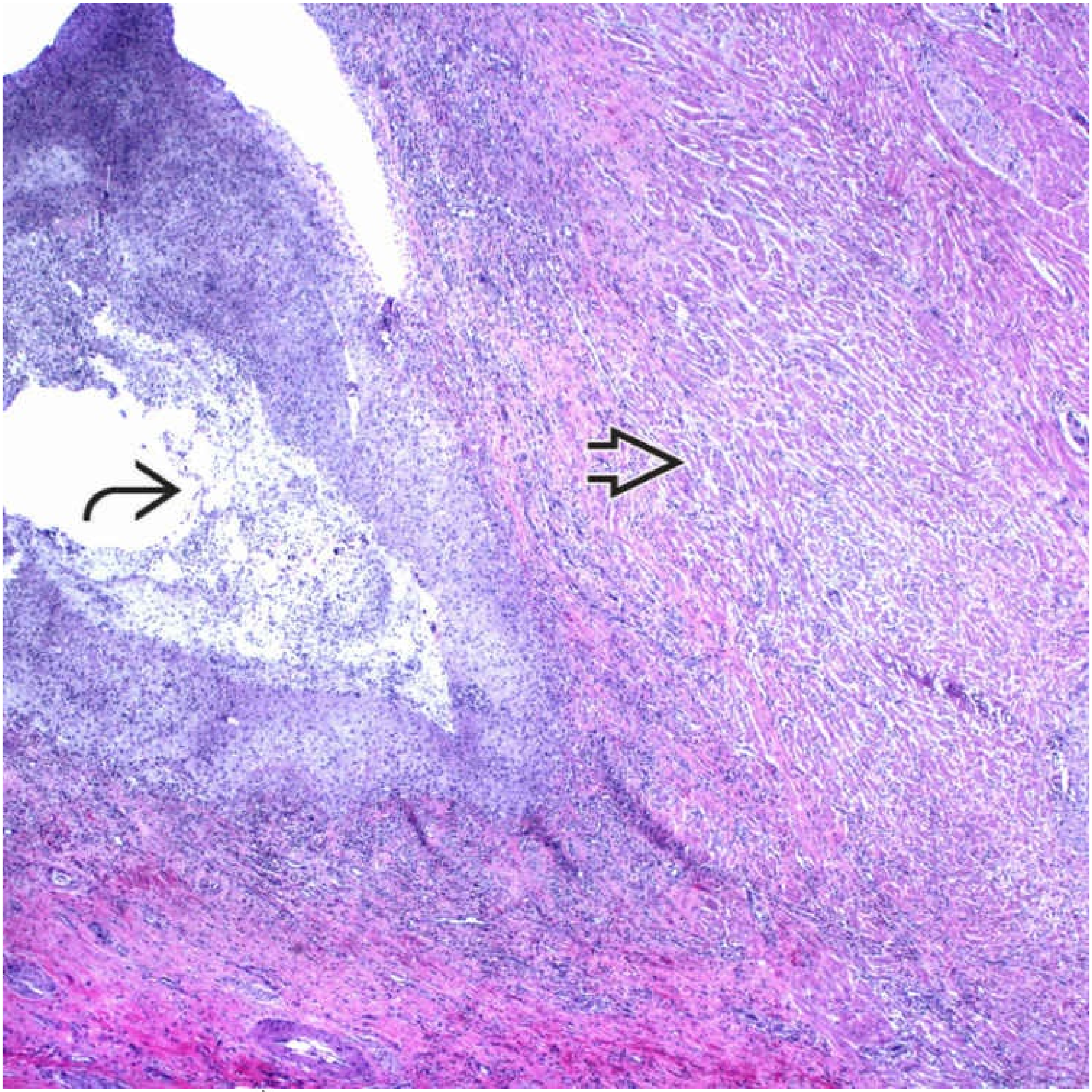
- Alcohol-related pancreatitis diffusely involves pancreas and lacks duodenal wall changes that are characteristic of groove pancreatitis

Autoimmune Pancreatitis

- Lacks paraduodenal accentuation of groove pancreatitis
  - Periductal inflammation, obliterative phlebitis, and storiform fibroinflammatory proliferation are characteristic of autoimmune pancreatitis
  - Either entirely absent or only focally seen in groove pancreatitis
- Elevated numbers of IgG4(+) plasma cells (> 10/HPF) are invariably seen in autoimmune pancreatitis

Pancreatic Adenocarcinoma

- Clinically and radiologically, groove pancreatitis may be indistinguishable from pancreatic carcinoma
  - Histologically, lack of malignancy is obvious
  - Although occasional reactive and entrapped ducts may appear worrisome



A paraduodenal cyst is seen, which is lined by inflammation and granulation tissue. The paraduodenal "mass" is composed predominantly of a thickened muscularis propria with severe fibrosis .

SELECTED REFERENCES

1. Lekkerkerker, SJ, et al. Clinical outcomes and prevalence of cancer in patients with possible groove pancreatitis. *J Gastroenterol Hepatol*. 2016. [ePub].
2. DeSouza, K, et al. Groove pancreatitis: a brief review of a diagnostic challenge. *Arch Pathol Lab Med*. 2015; 139(3):417–421.
4. Klöppel, G. Chronic pancreatitis, pseudotumors and other tumor-like lesions. *Mod Pathol*. 2007; 20(Suppl 1):S113–S131.
5. Adsay, NV, et al. Paraduodenal pancreatitis: a clinico-pathologically distinct entity unifying

"cystic dystrophy of heterotopic pancreas", "para-duodenal wall cyst", and "groove pancreatitis". *Semin Diagn Pathol*. 2004; 21(4):247–254.

3. de Tejada, AH, et al. Endoscopic and EUS features of groove pancreatitis masquerading as a pancreatic neoplasm. *Gastrointest Endosc*. 2008; 68(4):796–798.

Infectious Pancreatitis

KEY FACTS

Terminology

- Primary infection of pancreas by virus, bacteria, fungus, or parasite is very rare
  - Should be considered in immunocompromised patients with pancreatitis
  - Pancreatic involvement is usually mild in cases of systemic infection
- Acute infection of pancreas is usually secondary event
  - Occurs in 40-70% of patients with necrotizing pancreatitis
  - Usually due to gram-negative aerobic bacteria
    - May also be caused by fungal infection, typically *Candida*

Etiology/Pathogenesis

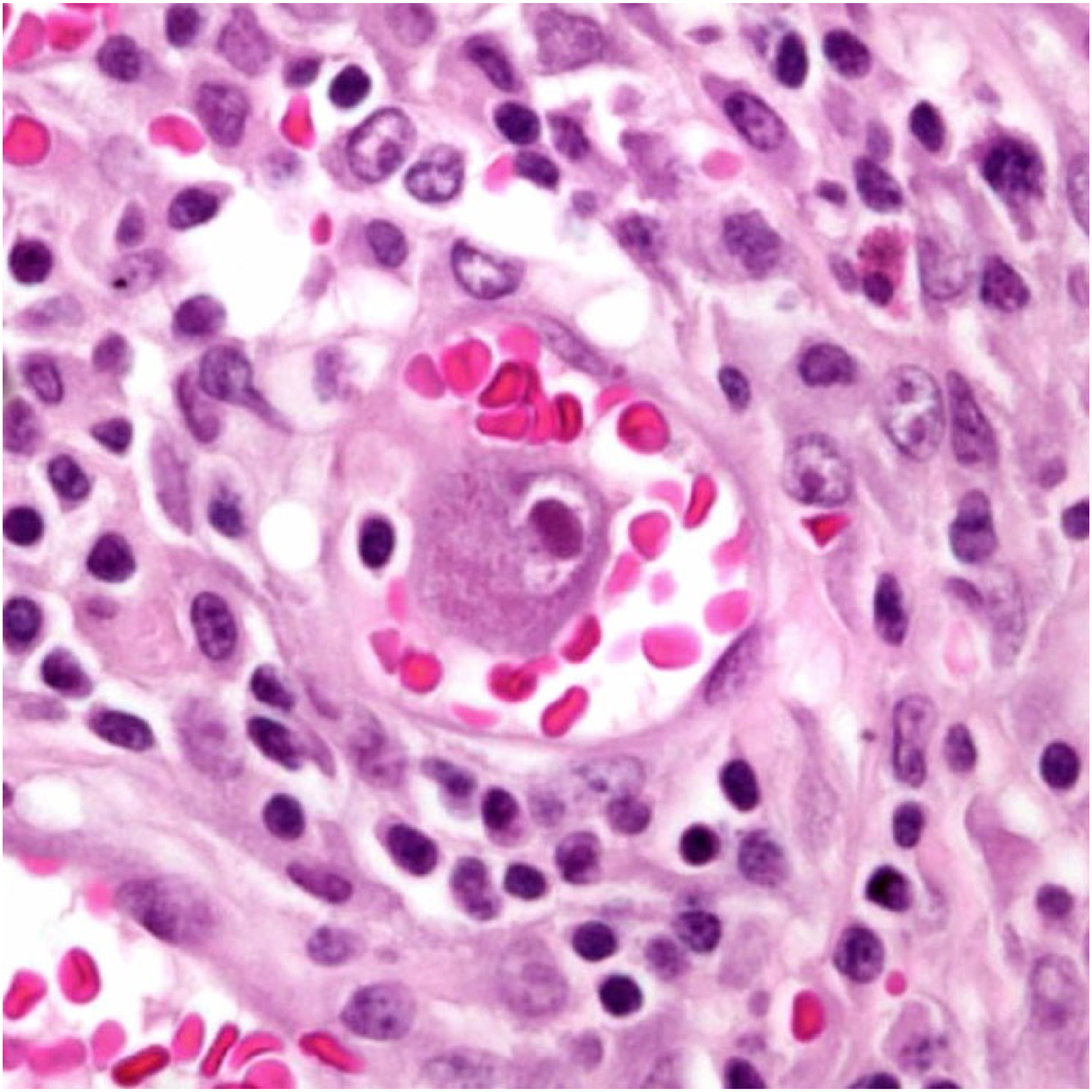
- Many different viruses, parasites, bacteria, and fungi
  - Viruses
  - Mumps, coxsackievirus, CMV
  - Mumps can cause severe pancreatitis
- Bacteria
- Many different pathogens, typically gram negative (*Escherichia coli*)
- Fungi
- Candida species most common
- Parasites
- *Ascaris*, *Clonorchis*, *Toxoplasma*
- Many cases associated with immune compromise

Clinical Issues

- Presentation, treatment, prognosis depend on specific infection and clinical scenario

Microscopic

• Gross and histologic findings are not well described



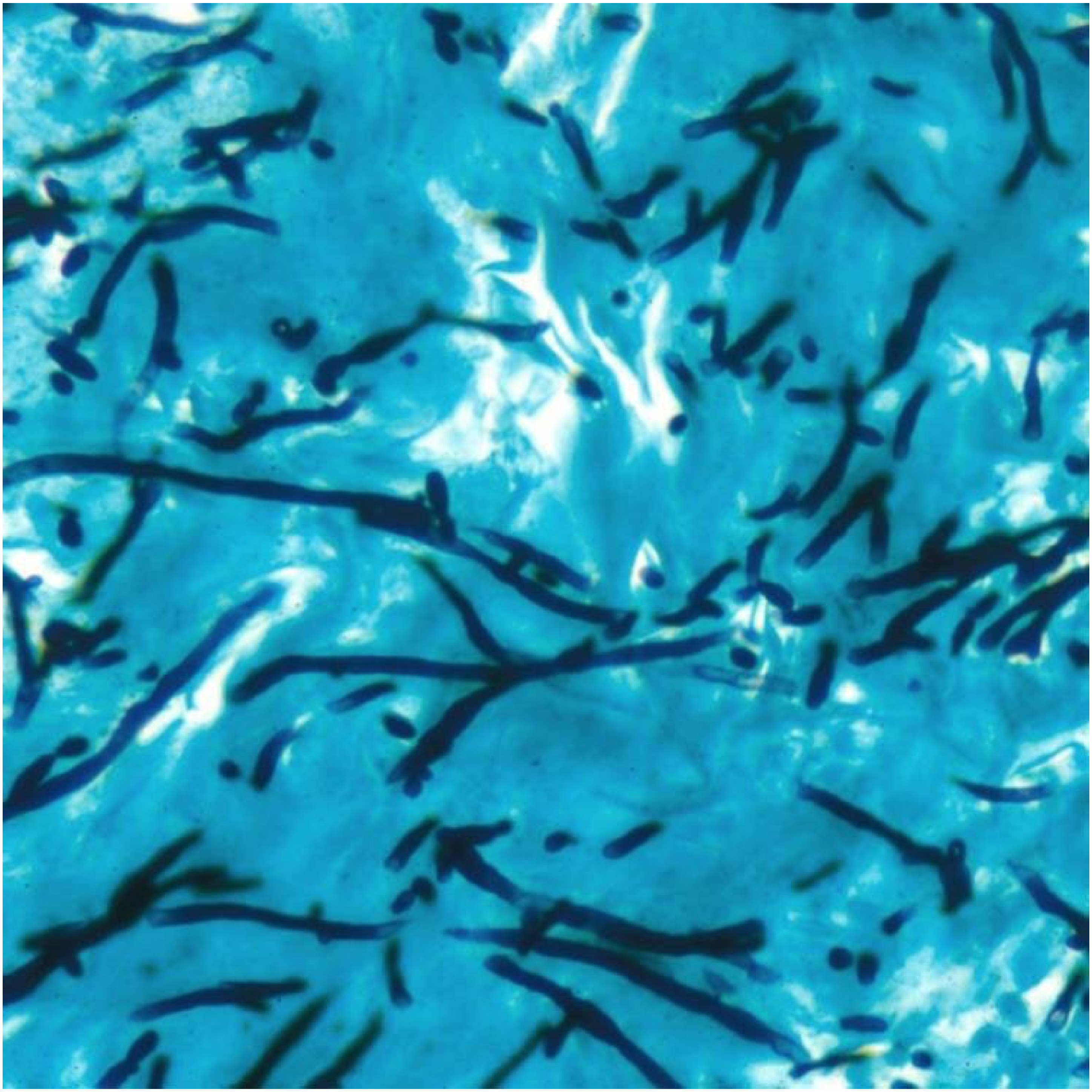
CMV

CMV infection of the pancreas is most often seen in immunocompromised patients, especially AIDS patients.

Ascaris

Ascaris lumbricoides can migrate into the pancreatic duct, causing an obstructive pancreatitis.

Echinococcus
Acute pancreatitis can follow rupture of a hepatic hydatid cyst into the bile ducts with secondary obstruction of the pancreatic ducts. Rarely, Echinococcus causes primary pancreatic infection.



Candida
Candida infection is the most common fungal infection complicating acute pancreatitis.

TERMINOLOGY

Definitions

- Acute infection of pancreas is usually secondary event
  - Occurs in 40-70% of patients with necrotizing pancreatitis
  - Usually due to gram-negative aerobic bacteria
  - Fungi (typically *Candida*) may also superinfect acute pancreatitis
- Primary infection of pancreas by virus, bacteria, fungus, or parasite is very rare
  - Pancreatic involvement is usually not significant in overall context of systemic infection

– Exception is mumps, which can cause severe pancreatitis

ETIOLOGY/PATHOGENESIS

Infectious Agents

- Viruses
  - Mumps
  - Coxsackievirus B
  - CMV
  – Usually seen in context of immunosuppression (AIDS or other causes) and in neonates
- EBV
- Rubella
- Arbovirus
- Fulminant hepatitis B
- Parasites
  - *Toxoplasma gondii*
  - *Clonorchis*
    – Migrates to pancreas from liver in ~ 1/3 of hepatic clonorchiasis cases
  - *Ascaris*
    – Can migrate into pancreatic duct, causing acute obstruction
  - *Echinococcus*
    – Very rare cause of pancreatitis
    – Hydatid cysts rupture in pancreas, leading to inflammation
- Bacteria
  - *Treponema pallidum* (syphilis)
  - *M. tuberculosis*
    – Pancreatic tuberculosis is rare but reported
  - *Leptospira* species (leptospirosis)
- Fungi
  - *Candida*
  - *Aspergillus*

CLINICAL ISSUES

Presentation

- Depends on specific infectious agent
- Patients with viral infections may have prodrome of diarrhea

Laboratory Tests

- Serologies, blood cultures, molecular tests for specific infectious organisms may be useful

Treatment

- Depends on specific infection

Prognosis

- Depends on specific infection
  - Pancreatic involvement is usually mild in cases of systemic infection
  - – Mumps can cause severe pancreatitis
  - – Abscesses, bacterial superinfection, and parenchymal atrophy are complications of echinococcal infection of pancreas

MACROSCOPIC

General Features

- Gross findings are not well described

MICROSCOPIC

Histologic Features

- Histologic findings are not well described in general
  - Spotty acinar or ductal cell death, without fat necrosis or ductal necrosis, has been described in cases of viral pancreatitis and some bacterial infections
- Viral inclusions, parasites, fungi, or bacteria may be seen in some cases

DIFFERENTIAL DIAGNOSIS

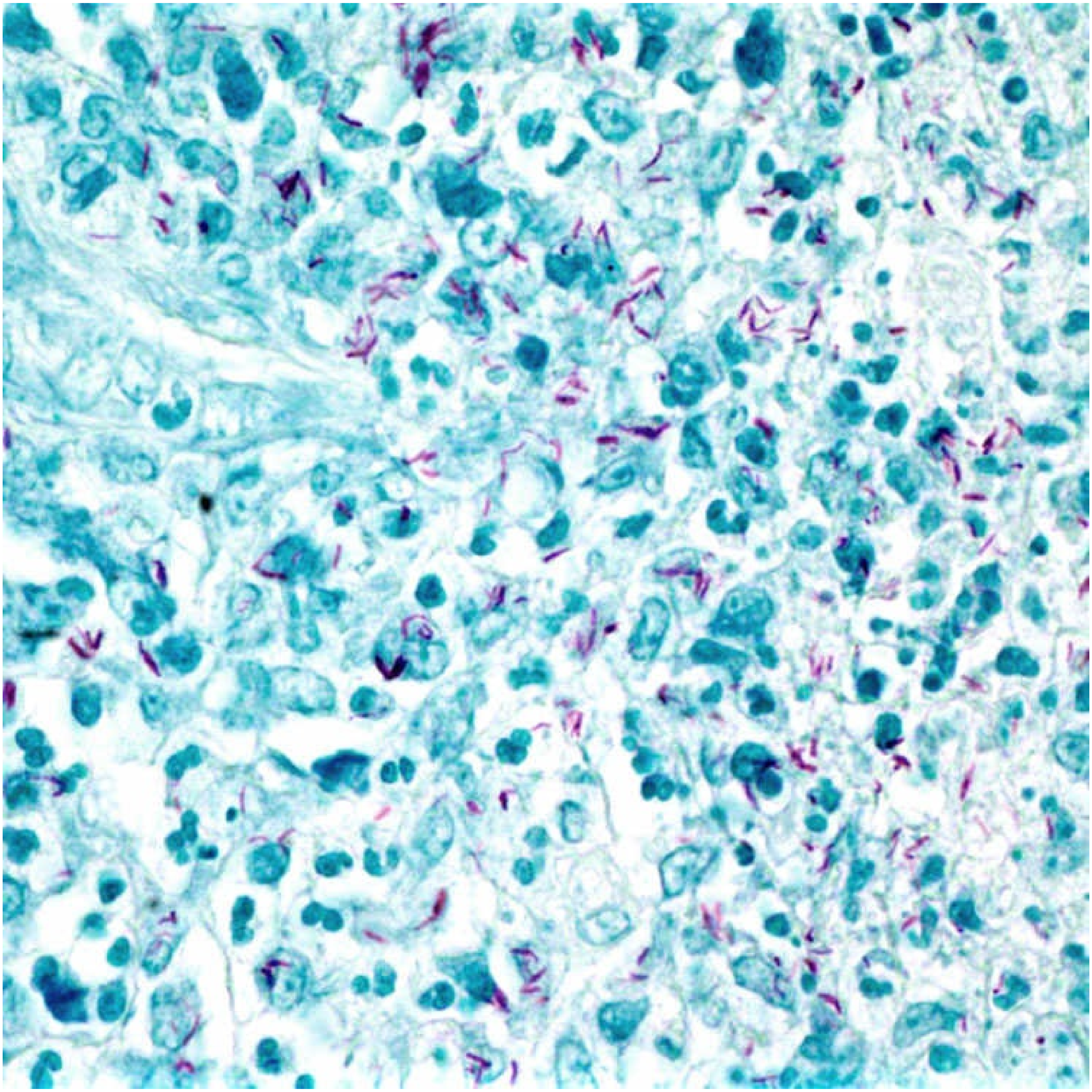
Other Causes of Acute Pancreatitis

- Alcohol
- Gallstones/obstruction
- Hyperlipidemia
- Drugs
- Anatomic abnormalities

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Very rare, but infection should be considered in immunocompromised patients with pancreatitis
- Secondary infection of acute necrotizing pancreatitis is much more common



M. tuberculosis infection of the pancreas is rare, even in miliary disease.

SELECTED REFERENCES

1. Kochhar, R, et al. Fungal infections in severe acute pancreatitis. *J Gastroenterol Hepatol*. 2011; 26(6):952–959.
2. Safioleas, MC, et al. Clinical considerations of primary hydatid disease of the pancreas. *Pancreatology*. 2005; 5(4-5):457–461.
3. Dalamaga, M, et al. Leptospirosis presenting as acute pancreatitis and cholecystitis. *J Med*. 2004; 35(1-6):181–185.
4. Dhall, JC, et al. Tuberculosis of the pancreas: a clinical rarity. *Am J Gastroenterol*. 1997; 92(1):172.

5. Parenti, DM, et al. Infectious causes of acute pancreatitis. *Pancreas*. 1996; 13(4):356–371.
6. Wilcox, CM, et al. Cytomegalovirus-associated acute pancreatic disease in patients with acquired immunodeficiency syndrome. Report of two patients. *Gastroenterology*. 1990; 99(1):263–267.
7. Joe, L, et al. Severe pancreatitis in an AIDS patient in association with cytomegalovirus infection. *South Med J*. 1989; 82(11):1444–1445.
8. Renner, IG, et al. Death due to acute pancreatitis. A retrospective analysis of 405 autopsy cases. *Dig Dis Sci*. 1985; 30(10):1005–1018.
9. Imrie, CW, et al. Coxsackie and mumpsvirus infection in a prospective study of acute pancreatitis. *Gut*. 1977; 18(1):53–56.

Pseudocysts

KEY FACTS

Terminology

• Pancreatic or peripancreatic collection of fluid rich in pancreatic enzymes

Etiology/Pathogenesis

• Occurs in patients with acute or chronic pancreatitis, biliary disease, surgery, or other trauma

Clinical Issues

• Spontaneous resolution occurs in 40-50% of patients
• Drainage (endoscopic, percutaneous, or surgical) if symptomatic, infected, or increasing in size

Macroscopic

• Usually unilocular cyst with thick, fibrous wall and shaggy, irregular inner surface
• Contain fluid, sometimes with blood and debris

Microscopic

• No epithelial lining
• Wall composed of granulation tissue and fibrosis
• Background pancreas will frequently show acute or chronic pancreatitis

Ancillary Tests

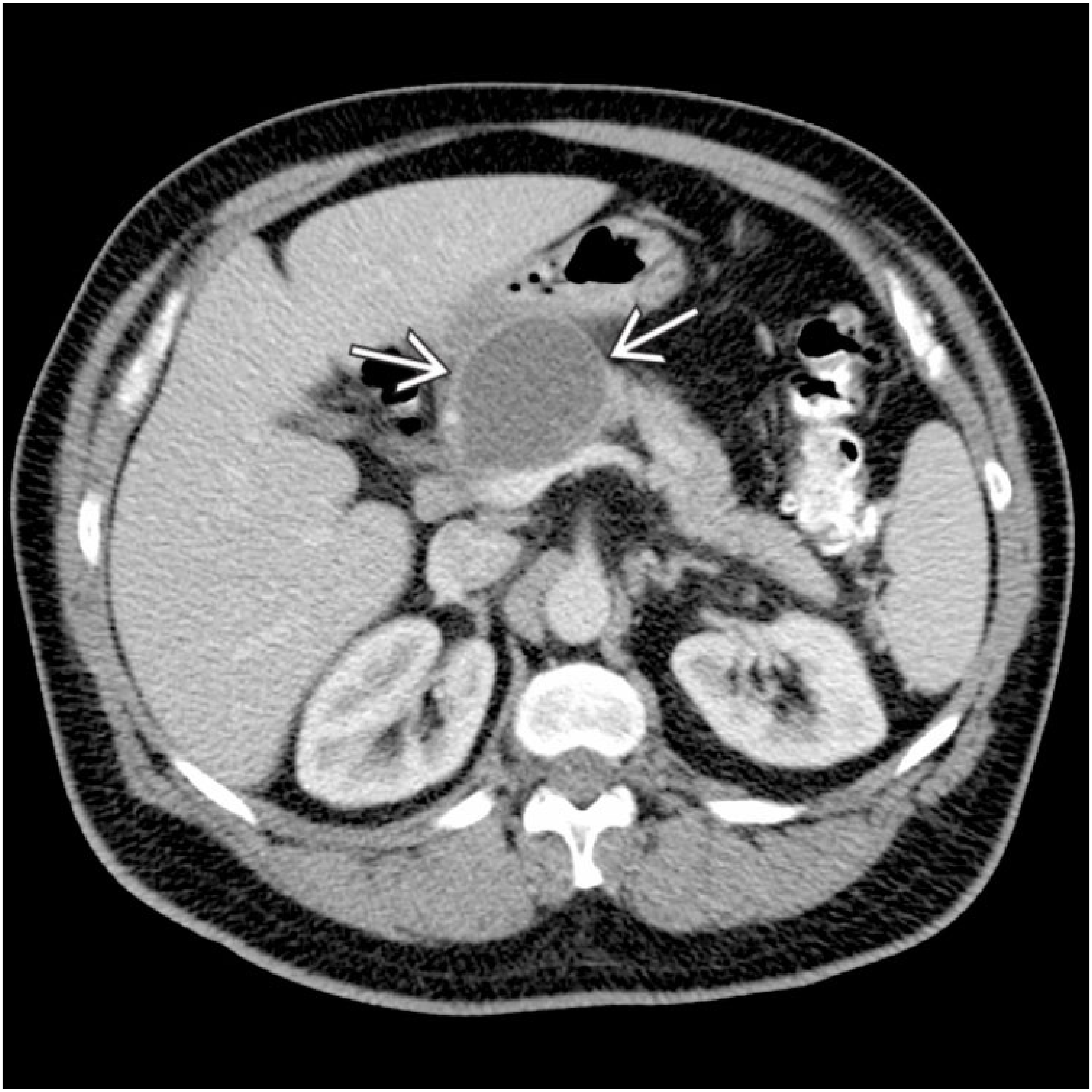
• Pseudocysts show elevated levels of amylase (> 250 IU/mL) and low levels of CEA (< 100 ng/mL)

Top Differential Diagnoses

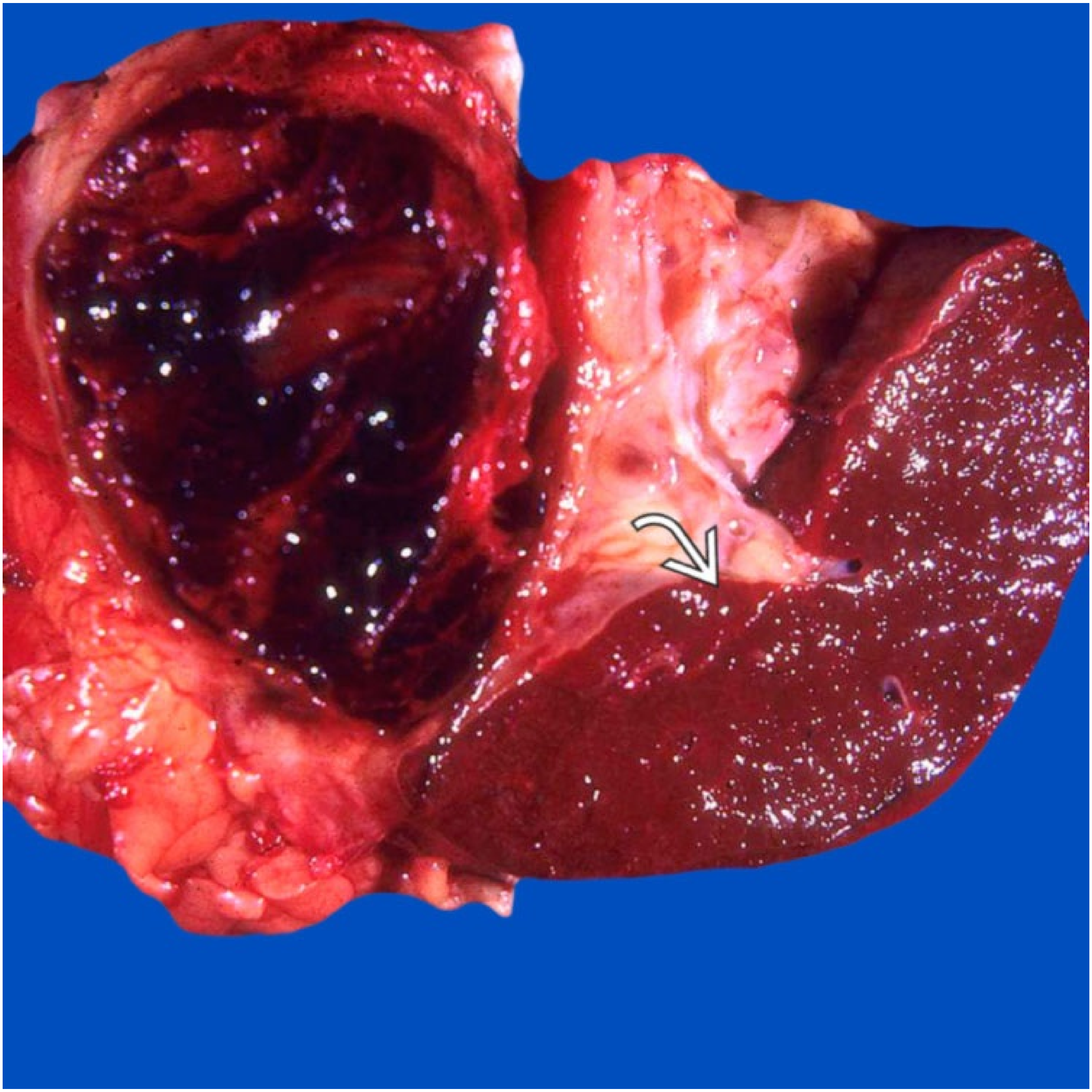
• Intraductal papillary-mucinous neoplasm and mucinous cystic neoplasm
• Cystic degeneration in adenocarcinoma or other pancreatic neoplasm

Diagnostic Checklist

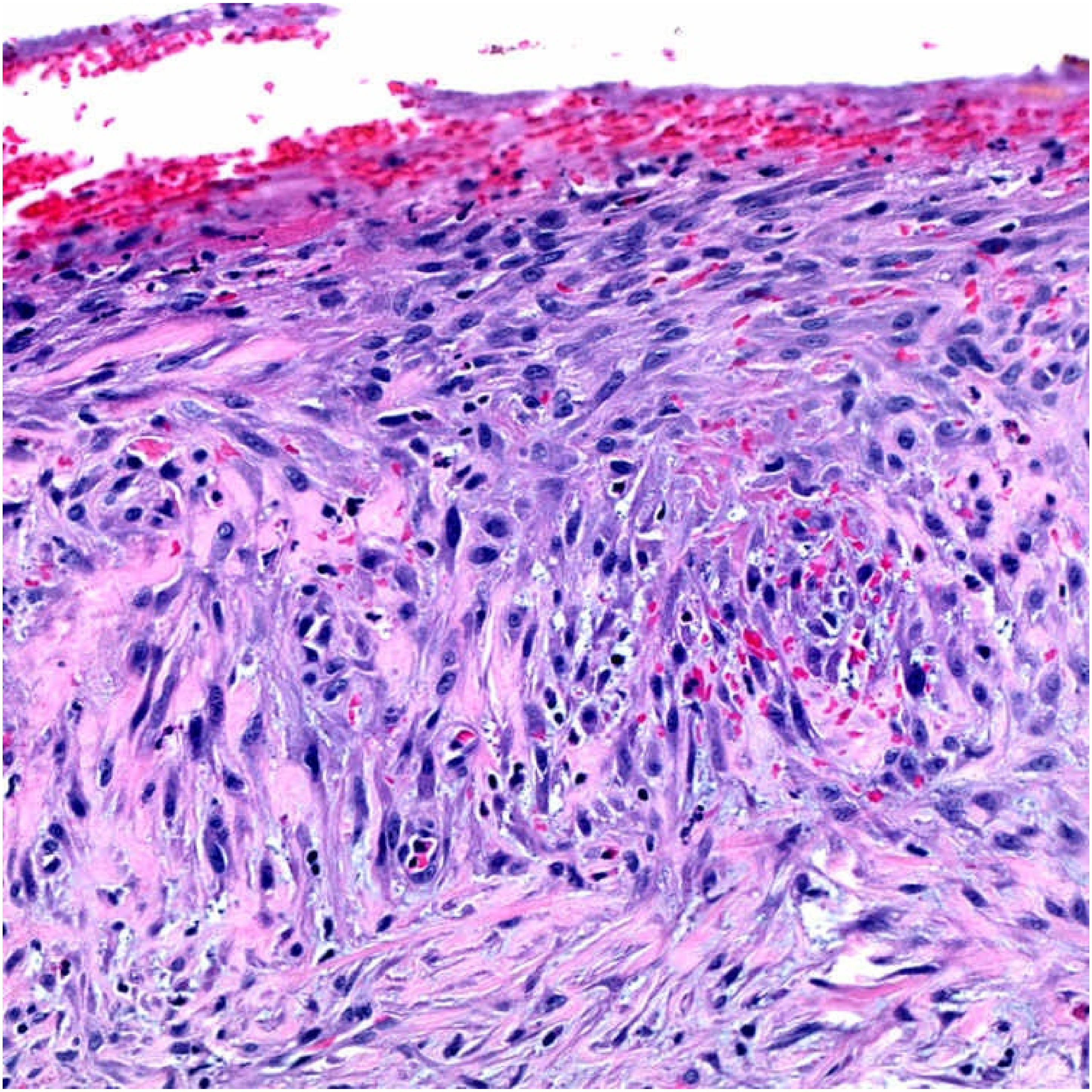
• Cystic lesion without epithelial lining arising in background of pancreatitis
• Entire cyst wall should be examined histologically before diagnosis of pseudocyst is rendered



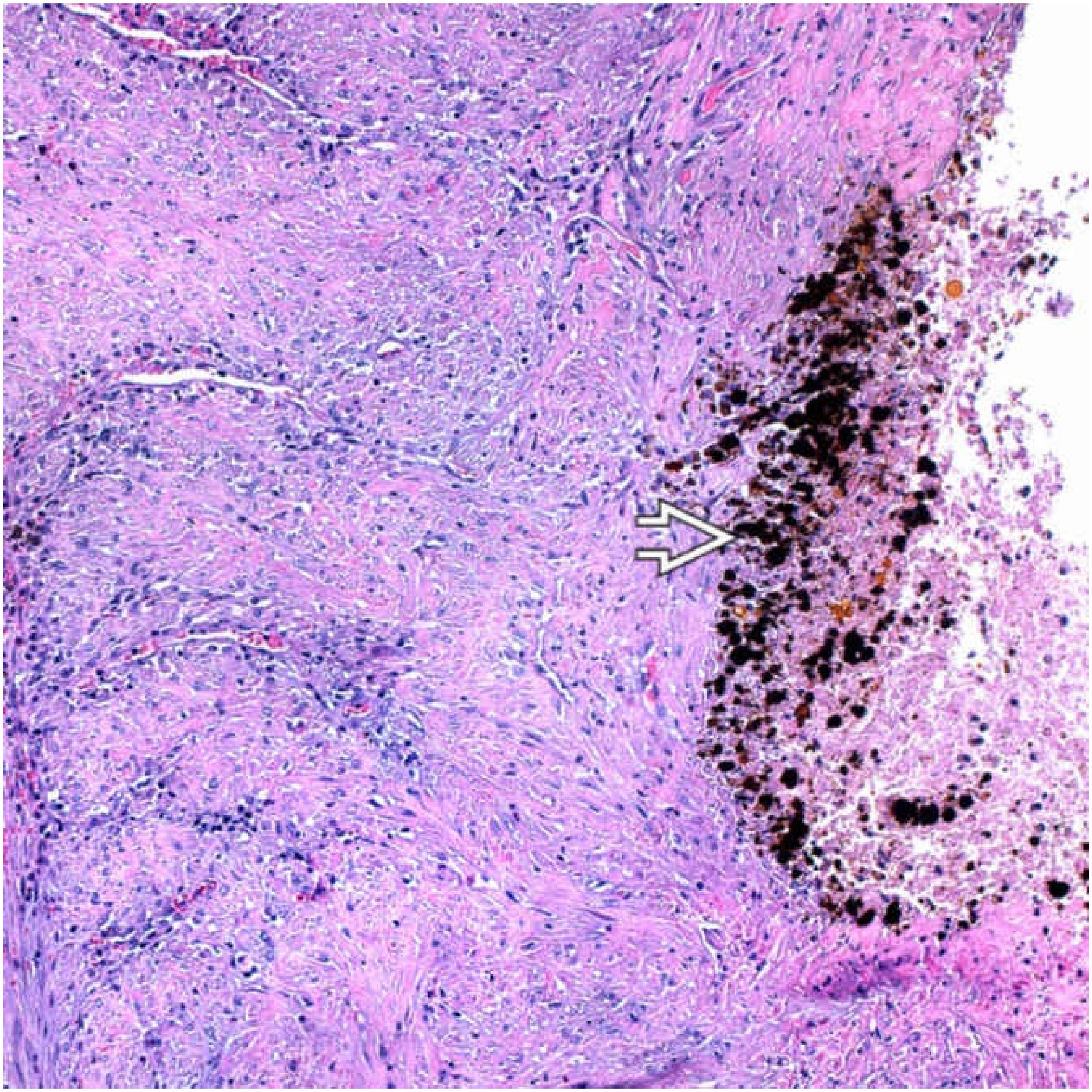
Pseudocyst on CT
CT shows a unilocular cyst located in the head of the pancreas, consistent with a pancreatic pseudocyst ⇨.



Pseudocyst With Hemorrhagic Fluid
Gross photograph shows a pseudocyst in the tail of the pancreas. The cyst is filled with hemorrhagic fluid. Note the adjacent spleen .



Pseudocyst Wall With Fibroblasts
Pseudocysts lack a true epithelial lining. The cyst wall shows an exuberant fibroblastic proliferation.



Hemosiderin and Fibrosis in Wall
The pseudocyst wall is composed of fibrosis and few scattered inflammatory cells. Note the hemosiderin in the lumen of the cyst.

TERMINOLOGY

Definitions

- Cystic collection of pancreatic or peripancreatic fluid rich in pancreatic enzymes

ETIOLOGY/PATHOGENESIS

Risk Factors

- Acute or chronic pancreatitis
- Can occur with biliary disease, surgery, or other trauma

- Rarely, may develop adjacent to pancreatic mass lesion, including adenocarcinoma

CLINICAL ISSUES

Epidemiology

- Incidence
  - Historically thought to represent 80% of all pancreatic cysts
  - High-resolution imaging now suggests neoplastic pancreatic cysts more common than pseudocysts
- Age
  - Young to middle-aged adults
- Sex
  - Female predominance associated with gallstone-related pancreatitis
  - Male predominance associated with alcohol-related pancreatitis

Presentation

- Recurrent abdominal pain, early satiety, nausea, and vomiting
- Typically in patient with history of pancreatitis

Treatment

- Spontaneous resolution occurs in 40-50% of patients
- Drainage (endoscopic, percutaneous, or surgical) if symptomatic, infected, or increasing in size

IMAGING

Radiographic Findings

- Round, fluid-filled structure surrounded by thick, dense wall seen on CT
- Endoscopic ultrasound may be useful to confirm and distinguish from other pancreatic cysts

MACROSCOPIC

General Features

- Usually unilocular cyst with thick, fibrous wall and shaggy, irregular inner surface
- Contain fluid, sometimes with blood and debris

Size

- Can measure > 20 cm

MICROSCOPIC

Histologic Features

- No epithelial lining
- Wall composed of granulation tissue and fibrosis
- Hemosiderin, blood pigments, and debris frequently seen in lumen and wall
- Background pancreas will frequently show acute or chronic pancreatitis

ANCILLARY TESTS

Fluid Analysis

- Cyst fluid contains elevated levels of amylase (> 250 IU/mL) and low levels of CEA (< 200 ng/mL)

DIFFERENTIAL DIAGNOSIS

Intraductal Papillary-Mucinous Neoplasm and Mucinous Cystic Neoplasm

- Absence of lining epithelium is key to diagnosis of pseudocyst
  - Both intraductal papillary-mucinous neoplasm and mucinous cystic neoplasm are lined by mucinous epithelium, at least focally
  - Ovarian-type stroma supports diagnosis of mucinous cystic neoplasm
    - Exuberant fibroblastic tissue in wall of pseudocyst occasionally mimics ovarian-type stroma
- Elevated cyst fluid CEA is strongly suggestive of mucinous neoplasm

Other Cystic Tumors

- Serous cystadenoma, solid pseudopapillary tumor, and cystic variant of pancreatic endocrine neoplasm
  - Unilocular serous cystadenomas may be largely denuded of neoplastic cells and mimic pseudocyst
  - Solid pseudopapillary tumors and pancreatic endocrine neoplasms show monotonous round neoplastic cells within cyst

Pseudocyst Adjacent to Pancreatic Neoplasms

- Pancreatic ductal adenocarcinomas can rarely show extensive cystic change
- Invasive carcinoma is generally recognized grossly adjacent to pseudocyst

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Cystic lesion in background of pancreatitis

Pathologic Interpretation Pearls

- Pseudocysts lack epithelial lining

- Examination of entire cyst wall required to exclude cystic neoplasm

SELECTED REFERENCES

1. Brugge, WR. Diagnosis and management of cystic lesions of the pancreas. *J Gastrointest Oncol*. 2015; 6(4):375–388.
2. Scheiman, JM, et al. American gastroenterological association technical review on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. *Gastroenterology*. 2015; 148(4):824–848. [.e22].
3. Basturk, O, et al. Pancreatic cysts: pathologic classification, differential diagnosis, and clinical implications. *Arch Pathol Lab Med*. 2009; 133(3):423–438.
4. Habashi, S, et al. Pancreatic pseudocyst. *World J Gastroenterol*. 2009; 15(1):38–47.
5. Klöppel, G. Pseudocysts and other non-neoplastic cysts of the pancreas. *Semin Diagn Pathol*. 2000; 17(1):7–15.

Diabetes Mellitus

KEY FACTS

Terminology

- Heterogeneous group of metabolic diseases characterized by hyperglycemia, generally classified as types 1 and 2
  - Type 1: Absolute insulin deficiency
  - Type 2: Insulin resistance and inadequate secretion

Etiology/Pathogenesis

- Unknown and multifactorial
  - Possible autoimmune causes
  - Some genetic causes
  - Diseases of exocrine pancreas

Clinical Issues

- Laboratory tests
  - Elevated random plasma and fasting glucose, hemoglobin A1c

Macroscopic

- Decreased size and weight (type 1 > type 2)

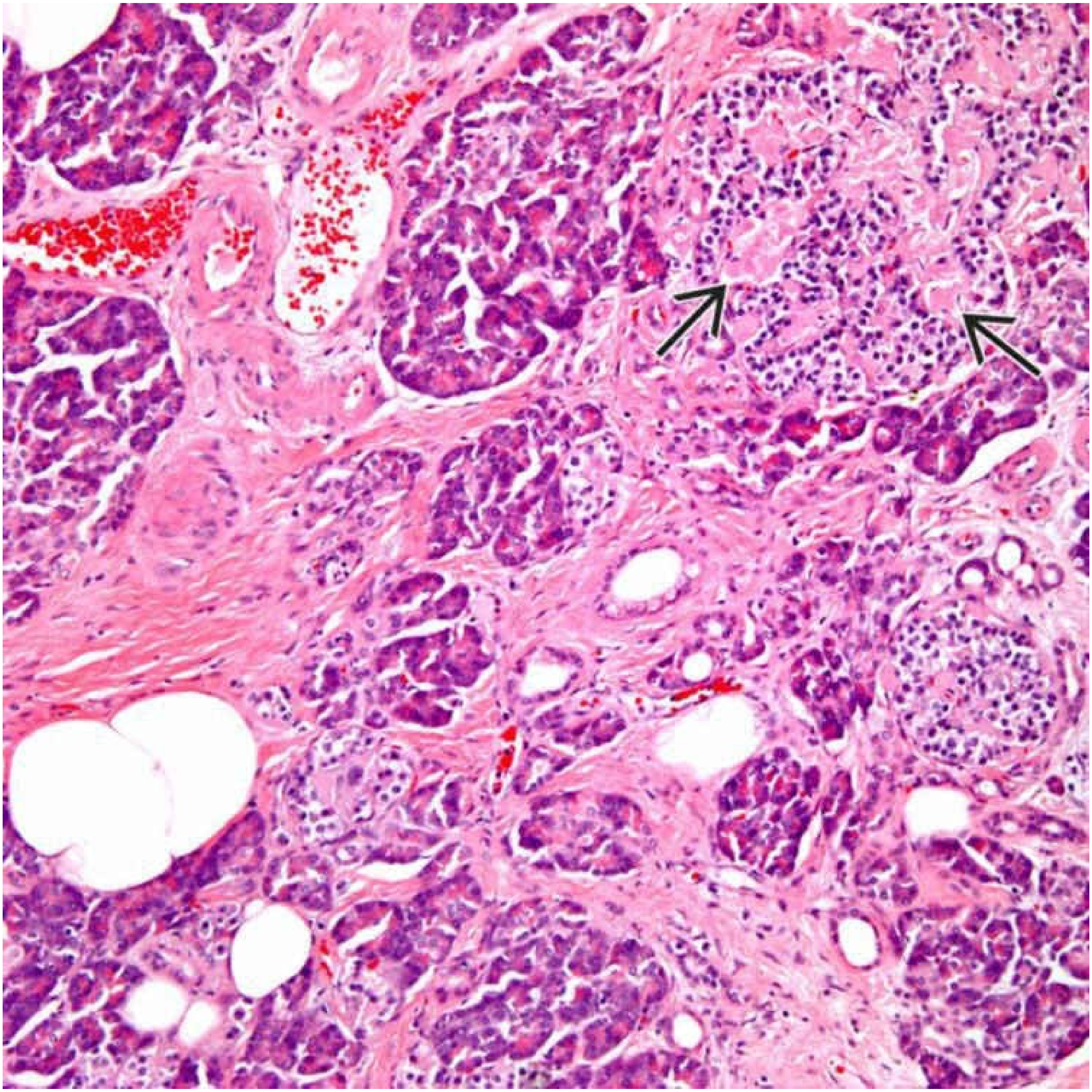
Microscopic

- Type 1
  - Variation in islet size and shape with irregularly shaped islets
  - Reduced or absent B cells
  - Variably present islet inflammation
  - Amyloidosis almost never seen in type 1 diabetes
- Type 2

  - Islet amyloidosis
  - Reduction in both A and B cells
  - Islets reduced in number but unchanged in size
- Both types
  - Interlobular and interacinar fibrosis, exocrine atrophy
  - Exocrine atrophy

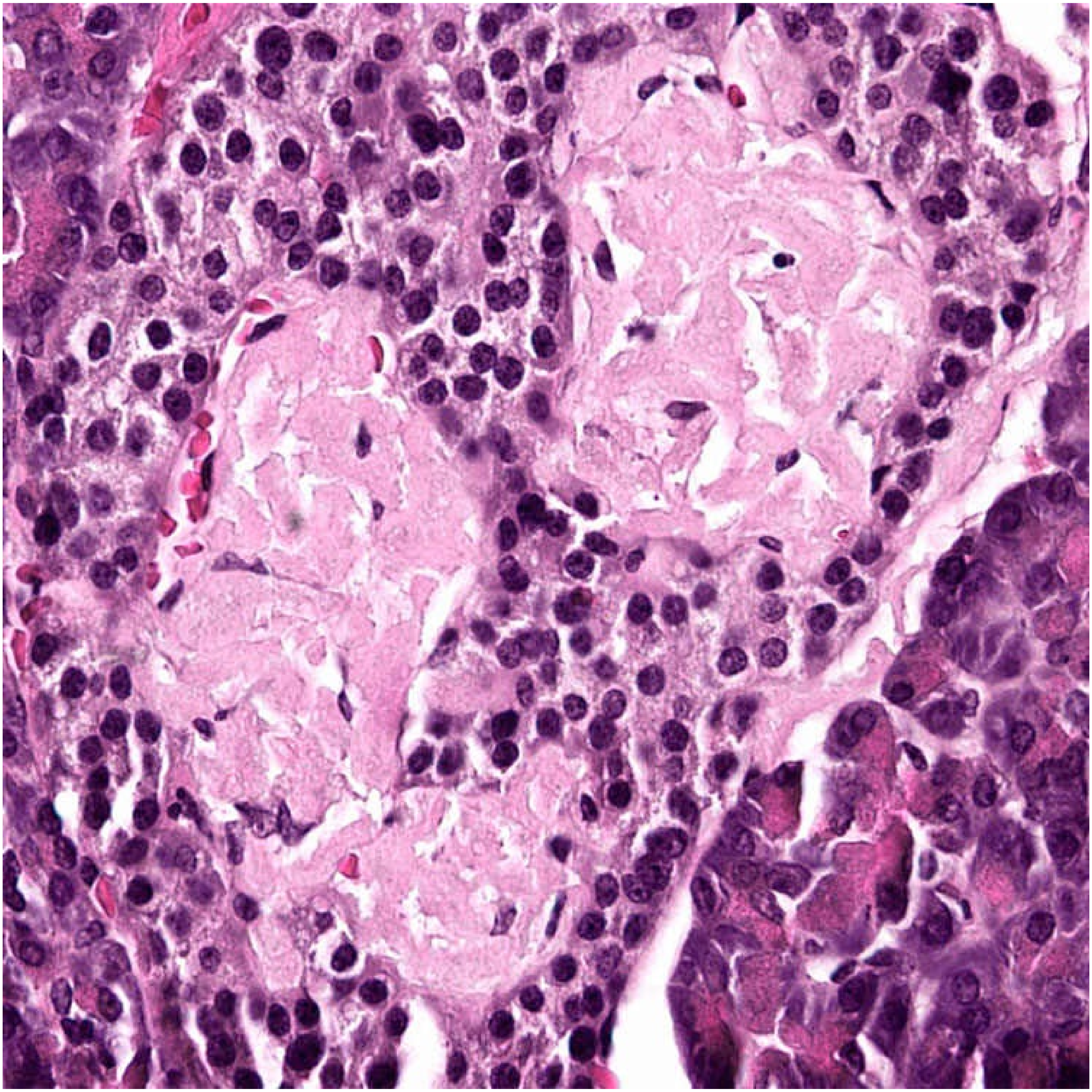
Top Differential Diagnoses

- Normal aging may also result in decreased size and weight of pancreas, islet amyloidosis

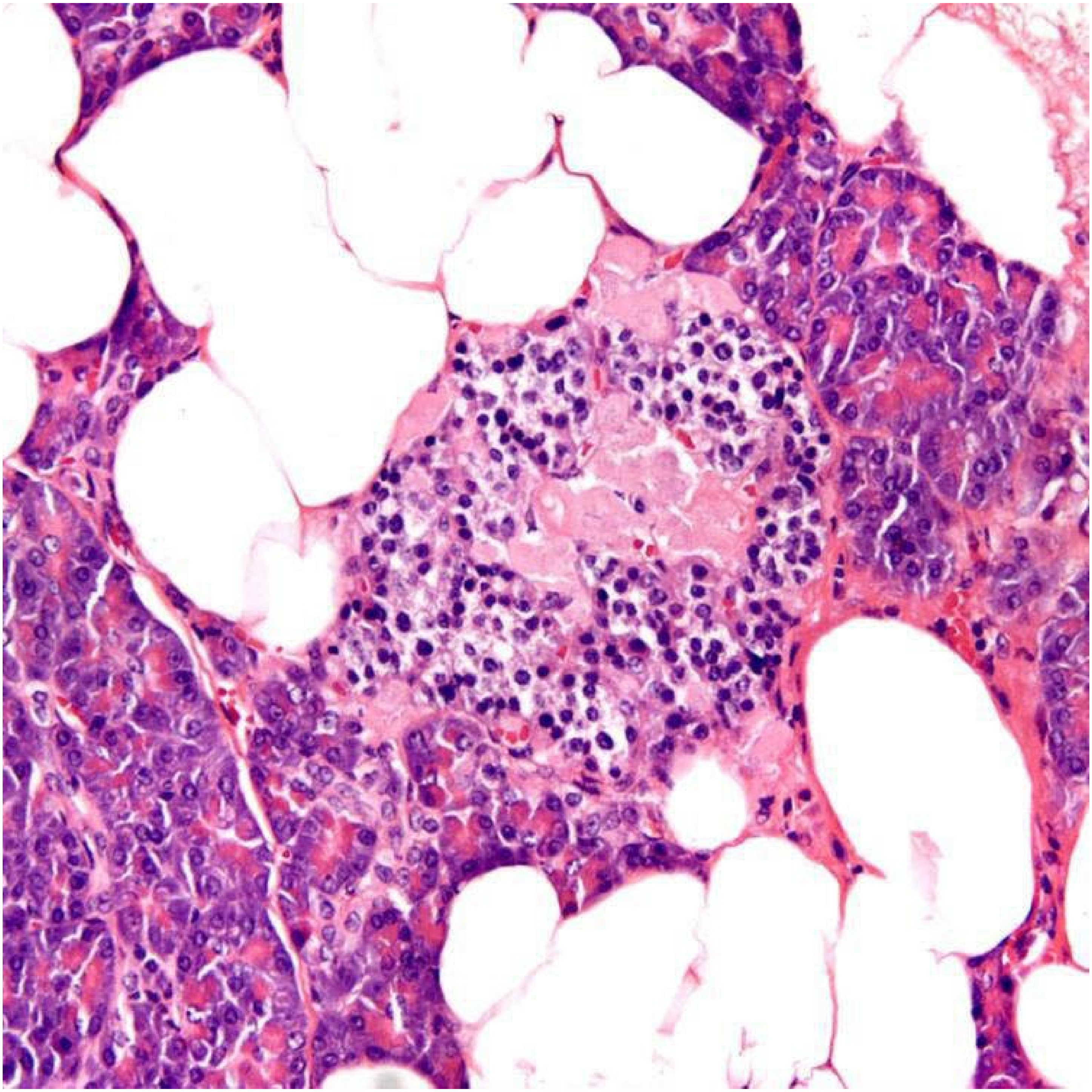


Fibrosis and Variably Sized Islets

This section from the pancreas of a patient with diabetes shows variably sized islets with focal amyloid deposition → and increased interacinar fibrosis.

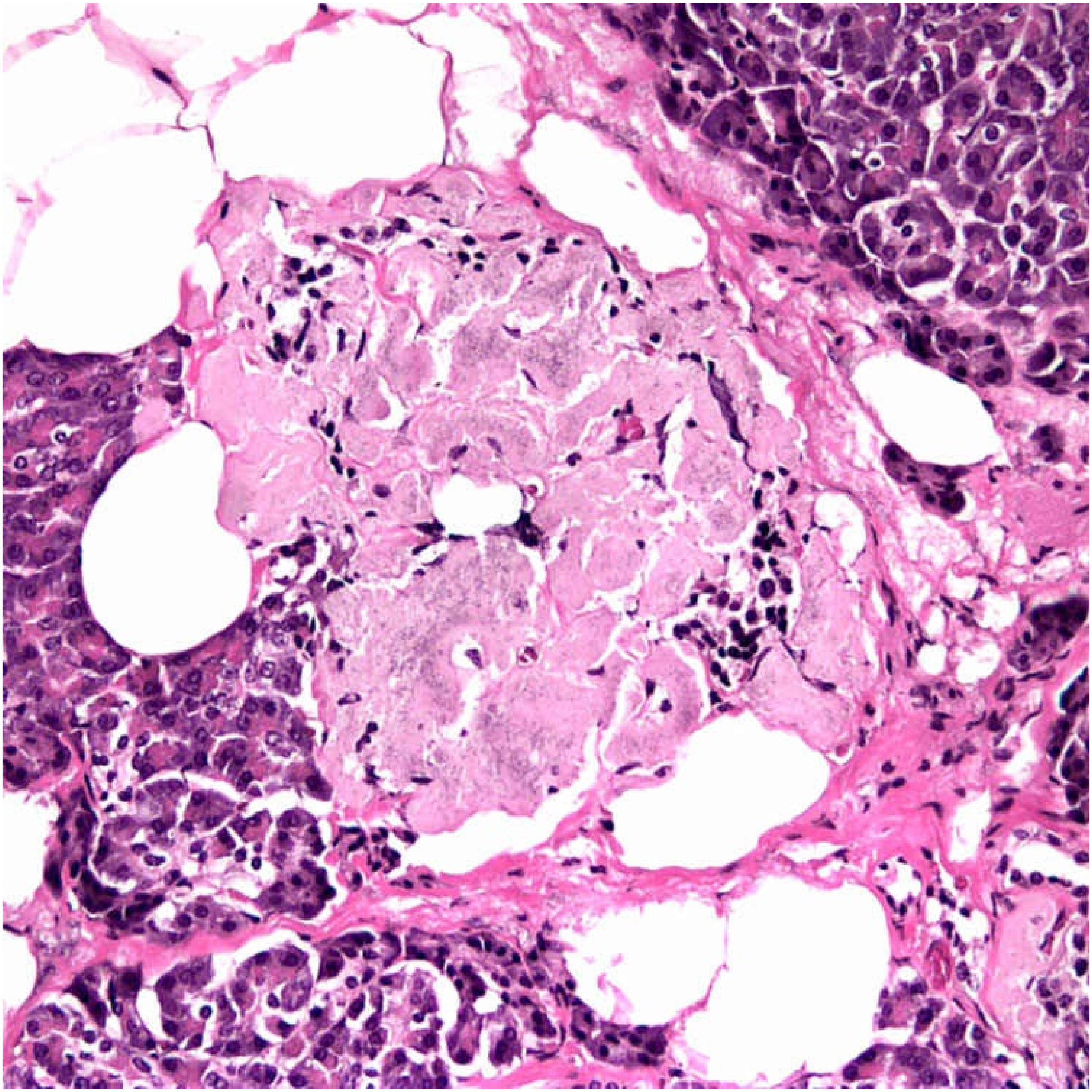


Islet With Amyloid
Dense nodules of amyloid are seen within an islet in this case of type 2 diabetes.



Fatty Infiltration

Fatty infiltration may also be a feature of diabetes seen in the pancreas, especially in type 2 diabetes. Note the central islet with amyloid deposition.



Islet Replacement by Amyloid
This islet is almost completely replaced by amyloid. There is also fatty infiltration of the pancreas.

TERMINOLOGY

Abbreviations

- Diabetes mellitus (DM)

Definitions

- Heterogeneous group of metabolic diseases characterized by hyperglycemia
  - Result of defects in insulin secretion, insulin activity, or both

- General classification
  - Type 1
    - – Absolute insulin deficiency
  - Type 2
    - – Insulin resistance and inadequate secretion resulting in relative insulin deficiency

ETIOLOGY/PATHOGENESIS

Unknown and Multifactorial

- Possible autoimmune causes
  - Some genetic causes (defects of B-cell function or insulin action)
  - Diseases of exocrine pancreas
  - Pancreatitis
  - Trauma/surgery
  - Cystic fibrosis
- Nonpancreatic endocrine diseases
- Drug or chemical-related causes
- Infections
- Gestational diabetes

CLINICAL ISSUES

Presentation

- Polyuria
- Polydipsia
- Unexplained weight loss

Laboratory Tests

- Elevated random plasma glucose (> 200 mg/dL)
- Elevated fasting plasma glucose (> 126 mg/dL)
- Abnormal glucose tolerance test
- Elevated hemoglobin A1c

Treatment

- Drugs
  - Exogenous insulin
  - Oral hypoglycemics
- Other
  - Weight reduction
  - Diet modification

Prognosis

- Chronic, progressive disease with multisystemic complications

MACROSCOPIC

Type 1 Diabetes

- Early in disease course
  - Normal size, weight, consistency of pancreas
- Later in disease course
  - Decrease in size and weight
    - May decrease by as much as 1/2 of normal
  - Firm consistency due to fibrosis
  - More extreme loss of size than seen in type 2 DM

Type 2 Diabetes

- Reduced size and weight of pancreas
  - Sometimes due to fatty infiltration (lipomatosis)

MICROSCOPIC

Histologic Features

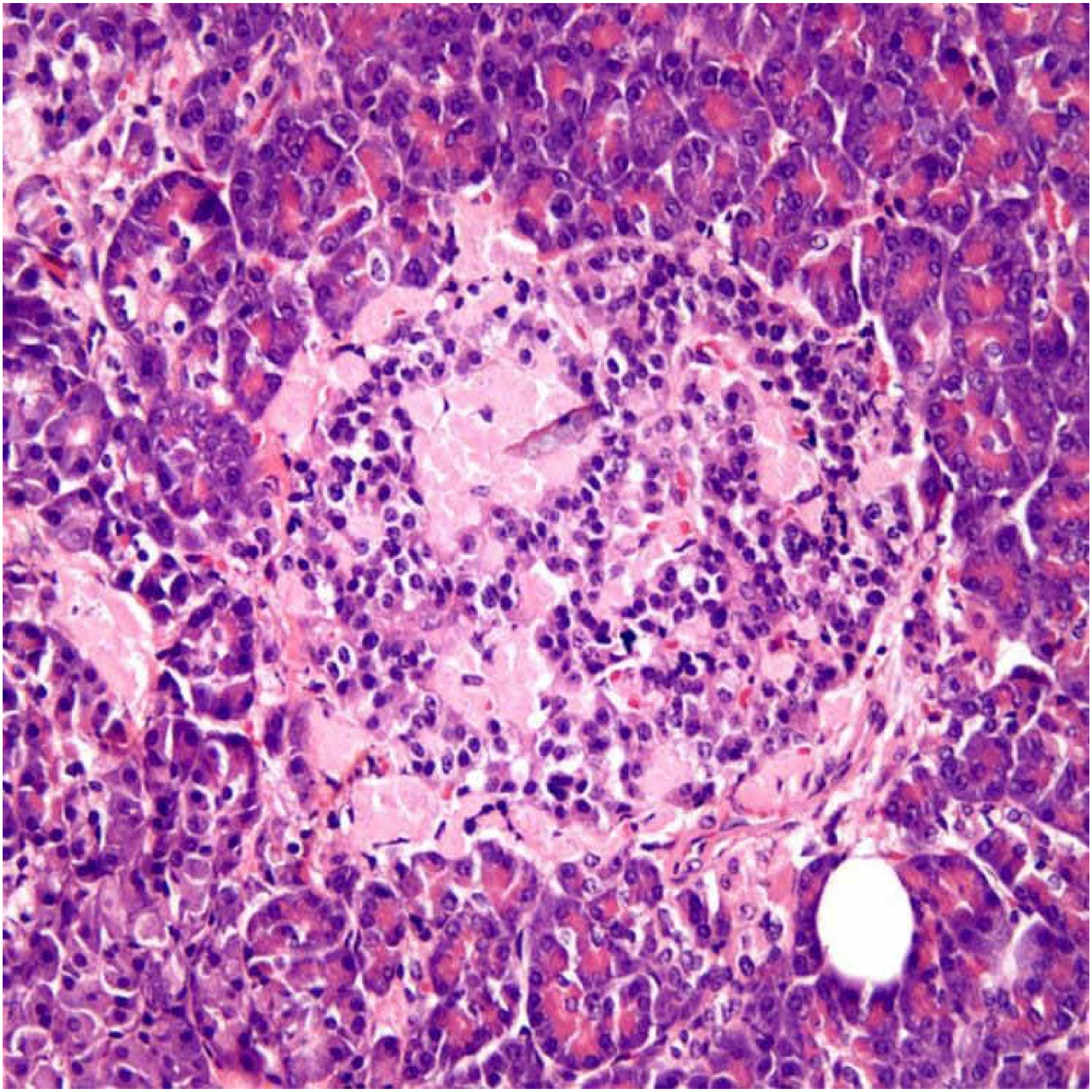
- Type 1
  - Very variable depending on duration of disease
  - Early in disease course (6 months to 1 year)
    - Variation in islet size and shape with irregularly shaped islets
    - Reduced B cells by immunohistochemistry
    - Lymphocytic inflammation of islets; may be patchy, not always present
  - Later in disease course (1 year and longer)
    - Interlobular and interacinar fibrosis
    - Exocrine atrophy
    - Complete or near absence of B cells
    - Variably present diabetic angiopathy
    - Islet amyloidosis is almost never seen in type 1 diabetes
- Type 2
  - Reduced acinar component
  - Perilobular and intraacinar fibrosis
  - Reduction in number and density of islets
    - Unchanged islet size
  - Reduction in both B and A cells by immunohistochemistry

- Amyloidosis of islets
  - Increases with length of disease duration, severity of disease, and treatment with insulin
  - Forms cords and nodules in perisinusoidal spaces
  - Represents concentrated form of islet amyloid polypeptide, which appears to be result of, rather than cause of, DM

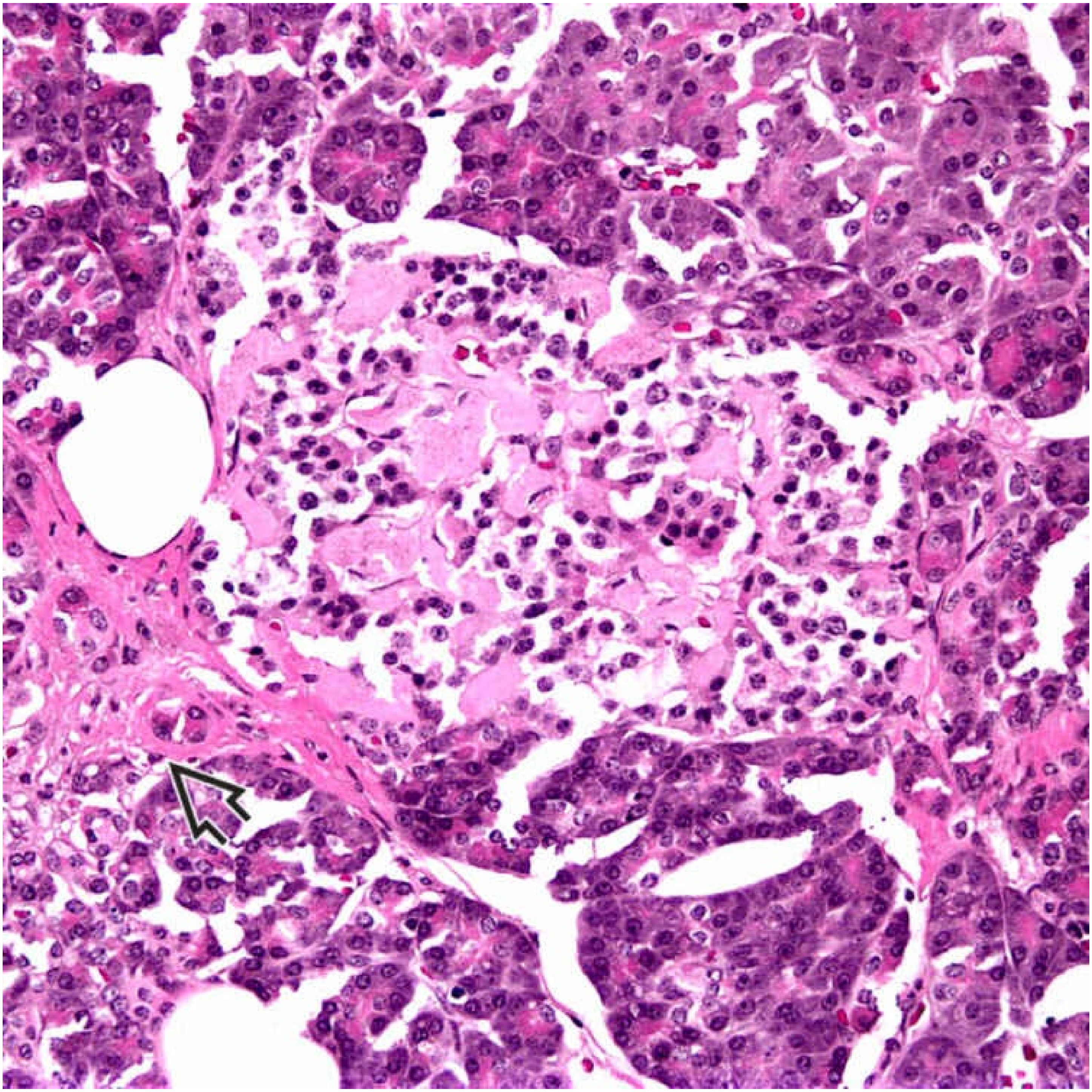
DIFFERENTIAL DIAGNOSIS

Normal Aging

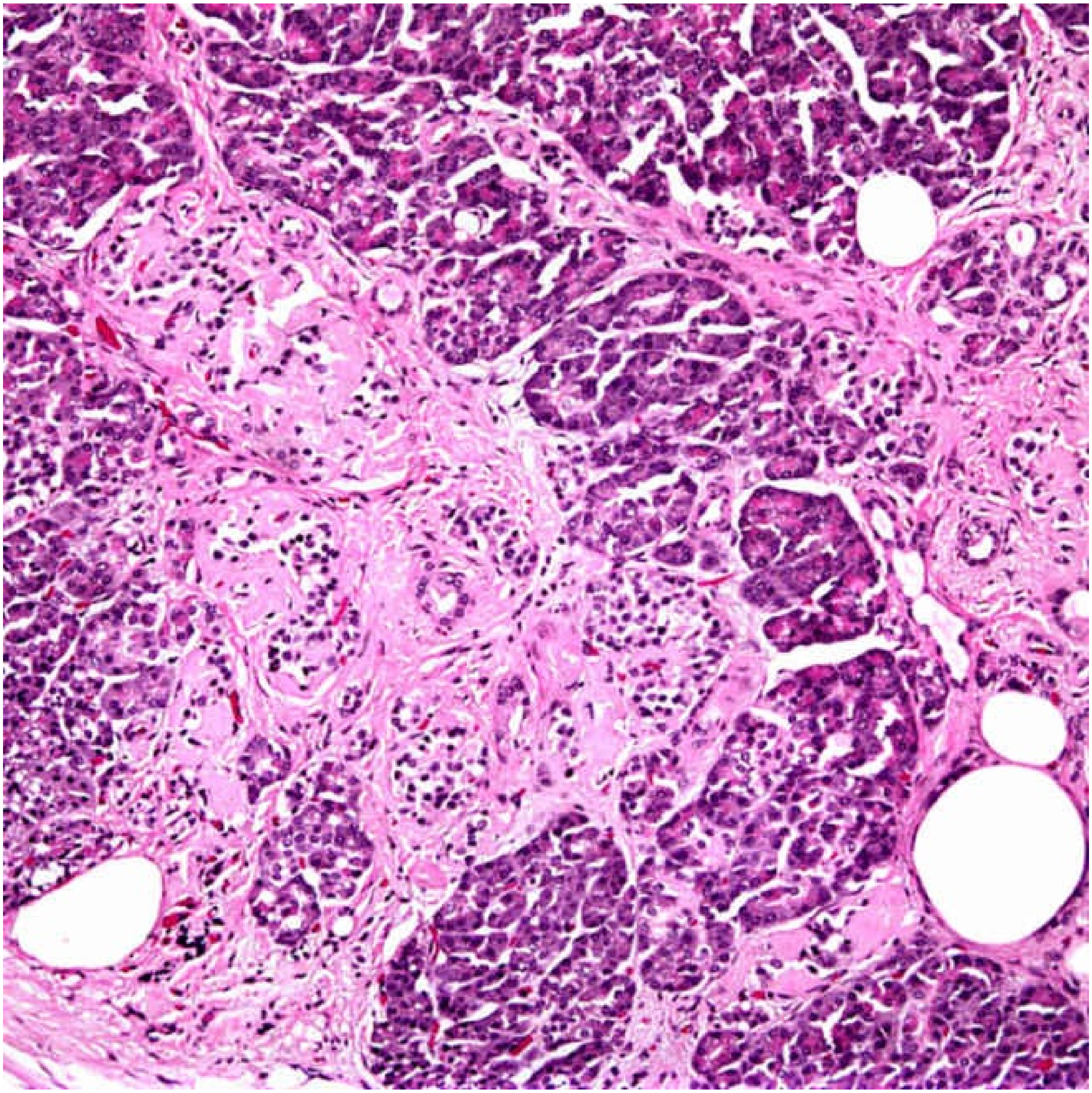
- Aging also causes decreased size and weight of pancreas
  - Islet amyloidosis also present in 4-23% of elderly persons without diabetes
  - These patients may be prediabetic
- Correlates with serum glucose tests, clinical data

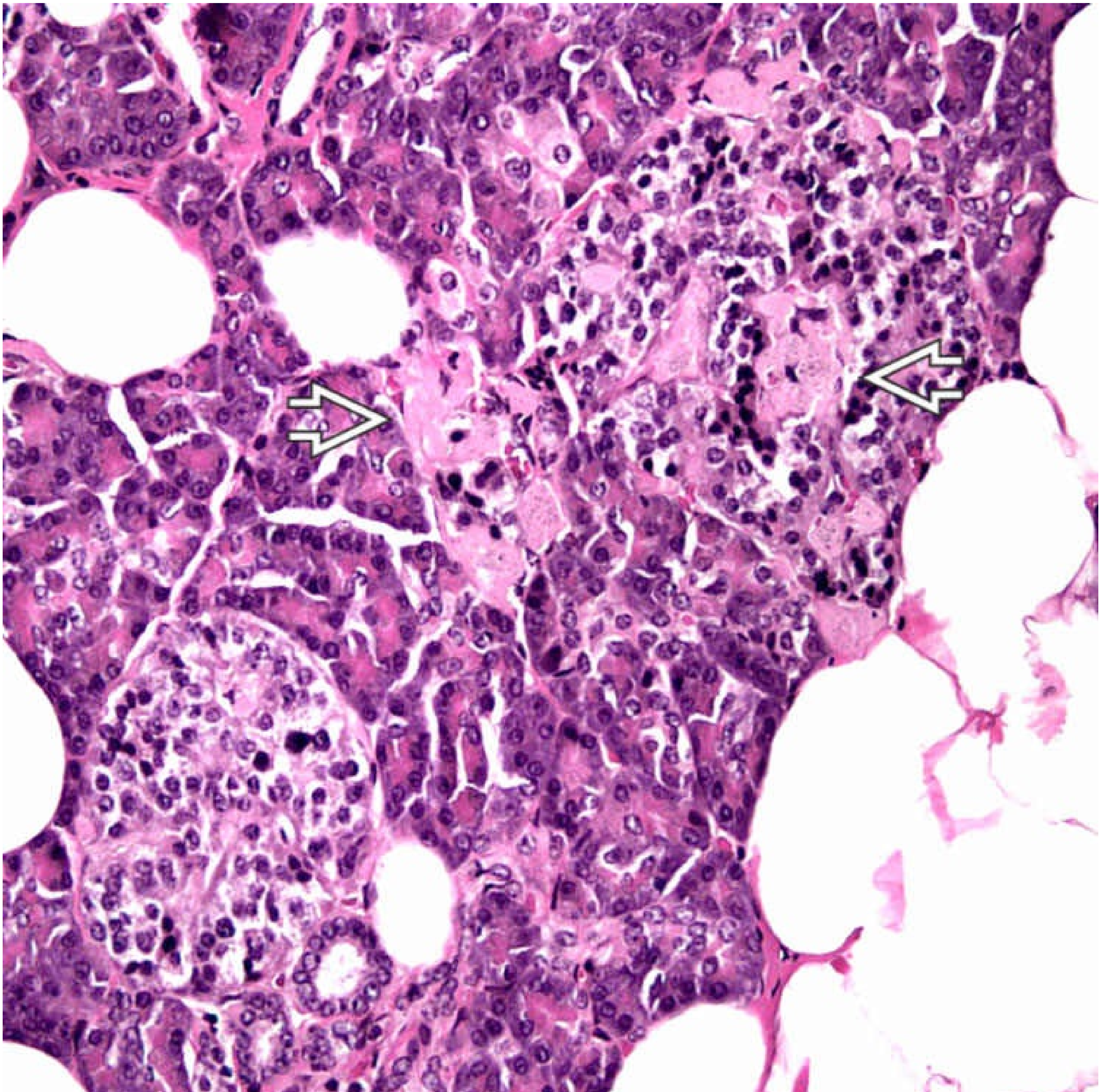


This islet contains amyloid as well as scattered lymphocytes. Lymphocytic inflammation within islets is variably present within the pancreata of type 1 diabetics.

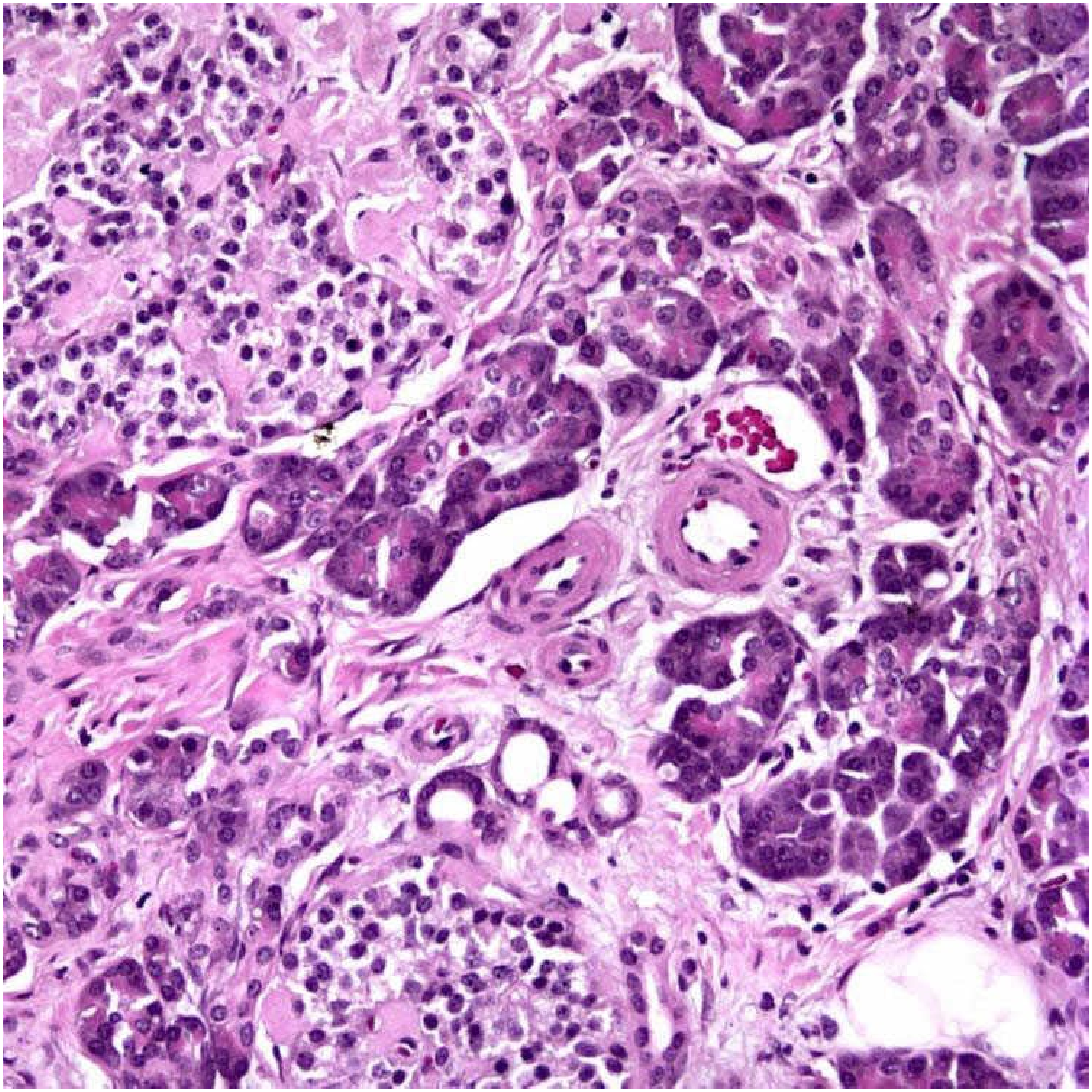


This islet cell contains small ribbons and nodules of amyloid. There is also focal fibrosis at the edge of the islet .


This case of type 2 diabetes shows intraacinar and perilobular fibrosis.



The islet to the left is unremarkable, while the islet to the right shows small nodules of amyloid ⇨. There is also fatty infiltration of the pancreas.


Small hyalinized arterioles are seen within the pancreas of this patient with type 1 diabetes (diabetic angiopathy).

SELECTED REFERENCES

1. Tomita, T. Islet amyloid polypeptide in pancreatic islets from type 2 diabetic subjects. *Islets*. 2012; 4(3):223–232.
2. Waguri, M, et al. Histopathologic study of the pancreas shows a characteristic lymphocytic infiltration in Japanese patients with IDDM. *Endocr J*. 1997; 44(1):23–33.
3. Alzaid, A, et al. The size of the pancreas in diabetes mellitus. *Diabet Med*. 1993; 10(8):759–763.
4. Pancreatic abnormalities in type 2 diabetes mellitus. *Lancet*. 1987; 2(8574):1497–1498.
5. Maloy, AL, et al. The relation of islet amyloid to the clinical type of diabetes. *Hum Pathol*. 1981; 12(10):917–922.

Lymphoepithelial Cysts

KEY FACTS

Clinical Issues

- Rare nonneoplastic pancreatic cystic lesions composed of squamous epithelial and lymphoid elements
- Resection is curative
- Malignant transformation has not been described
- Rare, accounting for 0.5% of pancreatic cystic lesions

Macroscopic

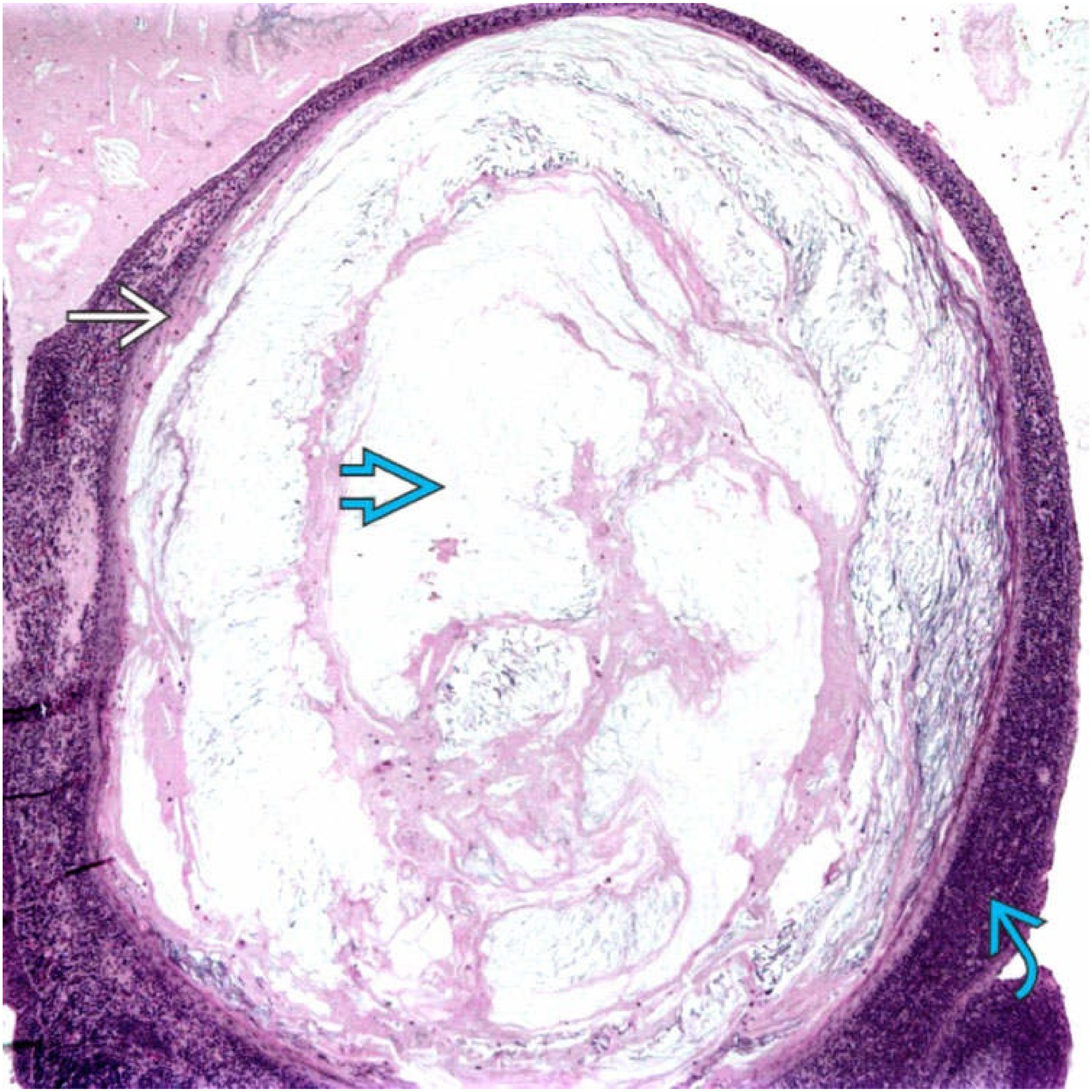
- Multilocular or unilocular cystic lesions
- Smooth or finely granular lining with serous to soft, friable/caseous contents
- Cyst wall may be surrounded by band of soft tan tissue

Microscopic

- Squamous-lined cysts with dense band of lymphoid tissue
  - Usually stratified squamous epithelium but cuboidal or transitional-like epithelium may be present
  - Dense distinct band of lymphoid tissue
- Other elements variably present
- Adjacent pancreas is often unremarkable

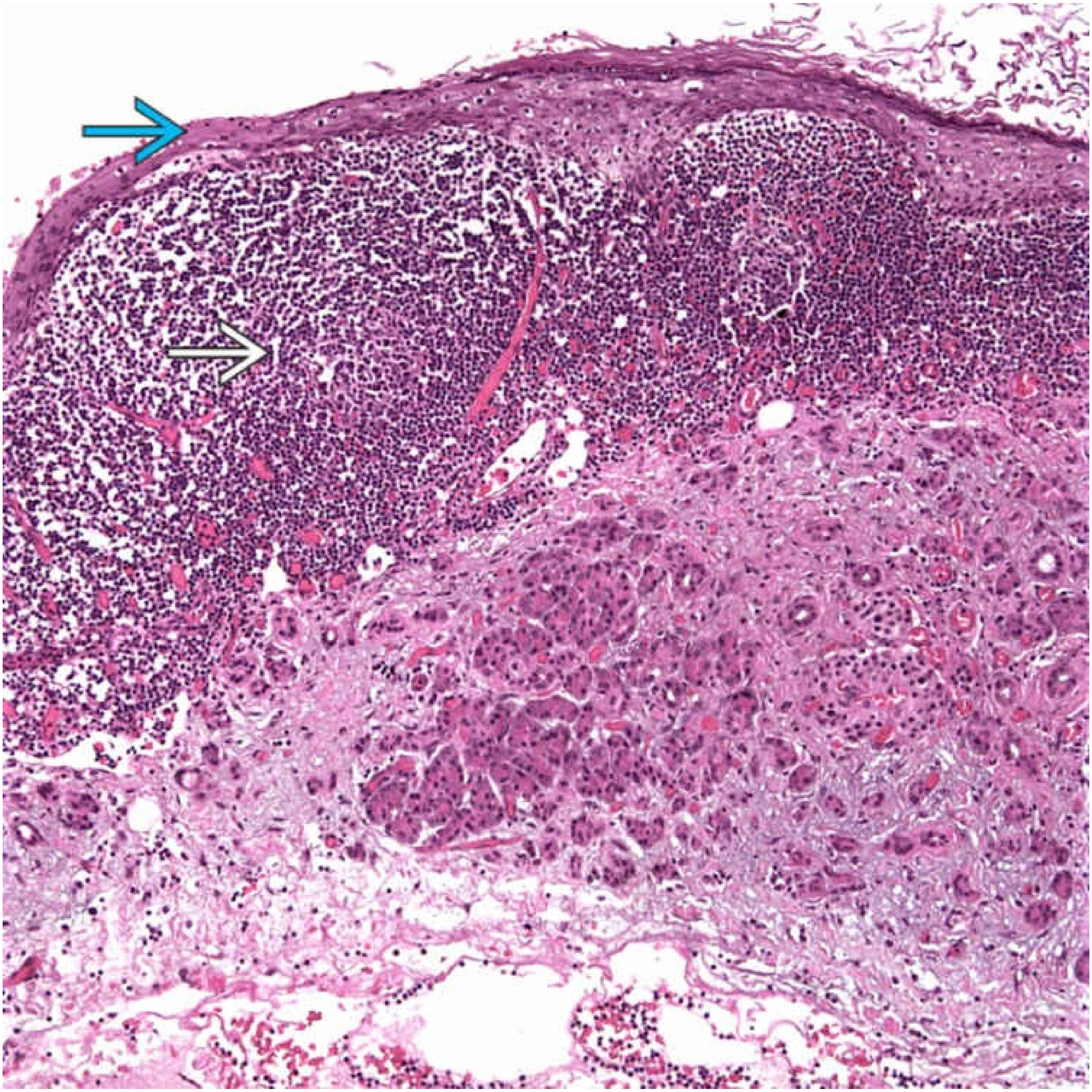
Top Differential Diagnoses

- Cystic entities lined by squamous epithelium
  - Epidermoid cyst in intrapancreatic spleen is surrounded by splenic tissue
  - Dermoid cyst has dermal appendages
  - Squamoid cyst is small without associated lymphoid tissue
- Lymphangioma has endothelial lining
  - Aggregates of lymphoid tissue rather than thick band of lymphoid tissue
- Multilocular cyst with endothelial lining
- Pseudocyst lacks epithelial lining



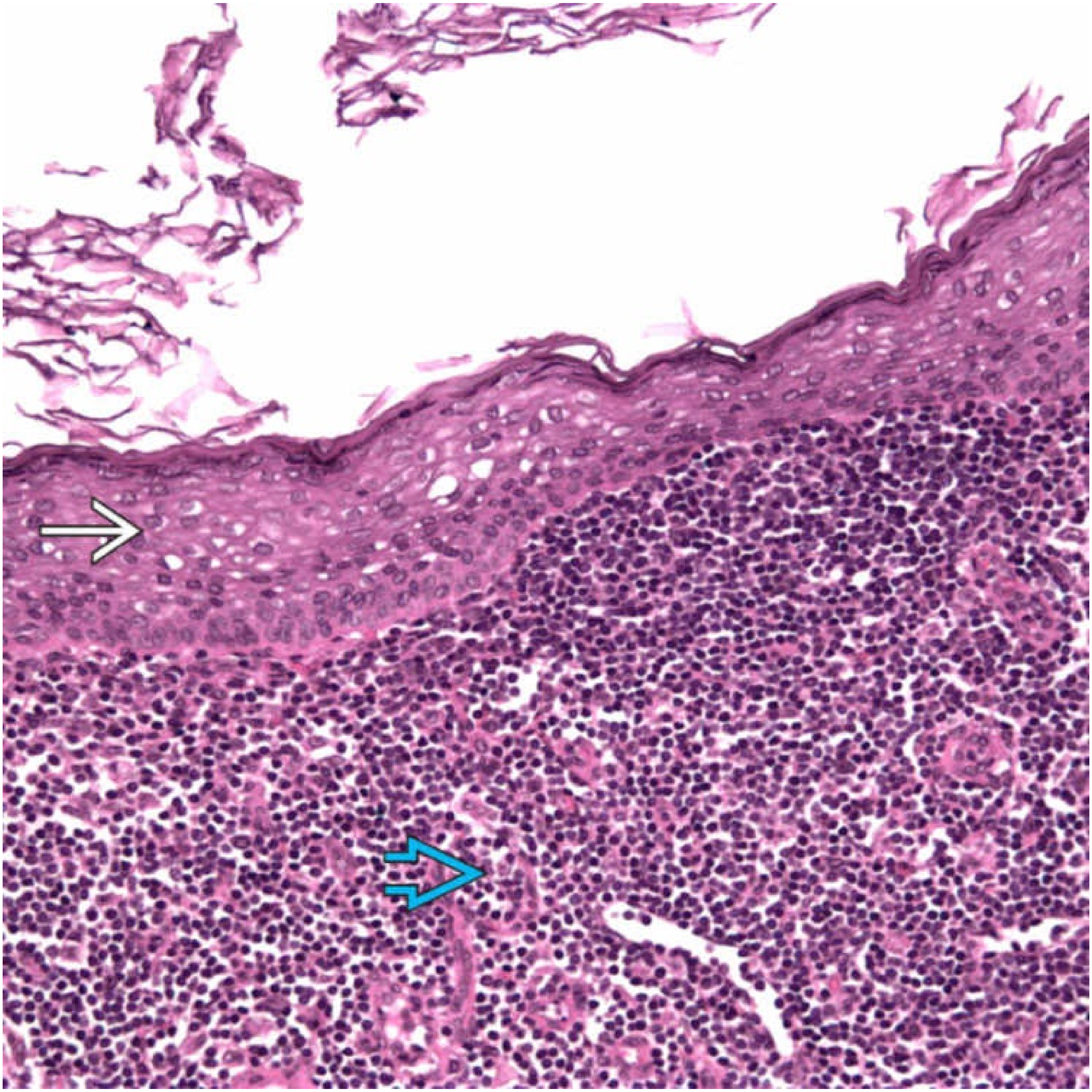
Squamous Lining and Keratinaceous Debris

Abundant keratinaceous debris is seen within this cyst locule. The cyst wall is composed of lymphoid tissue with a thin squamous epithelial lining .

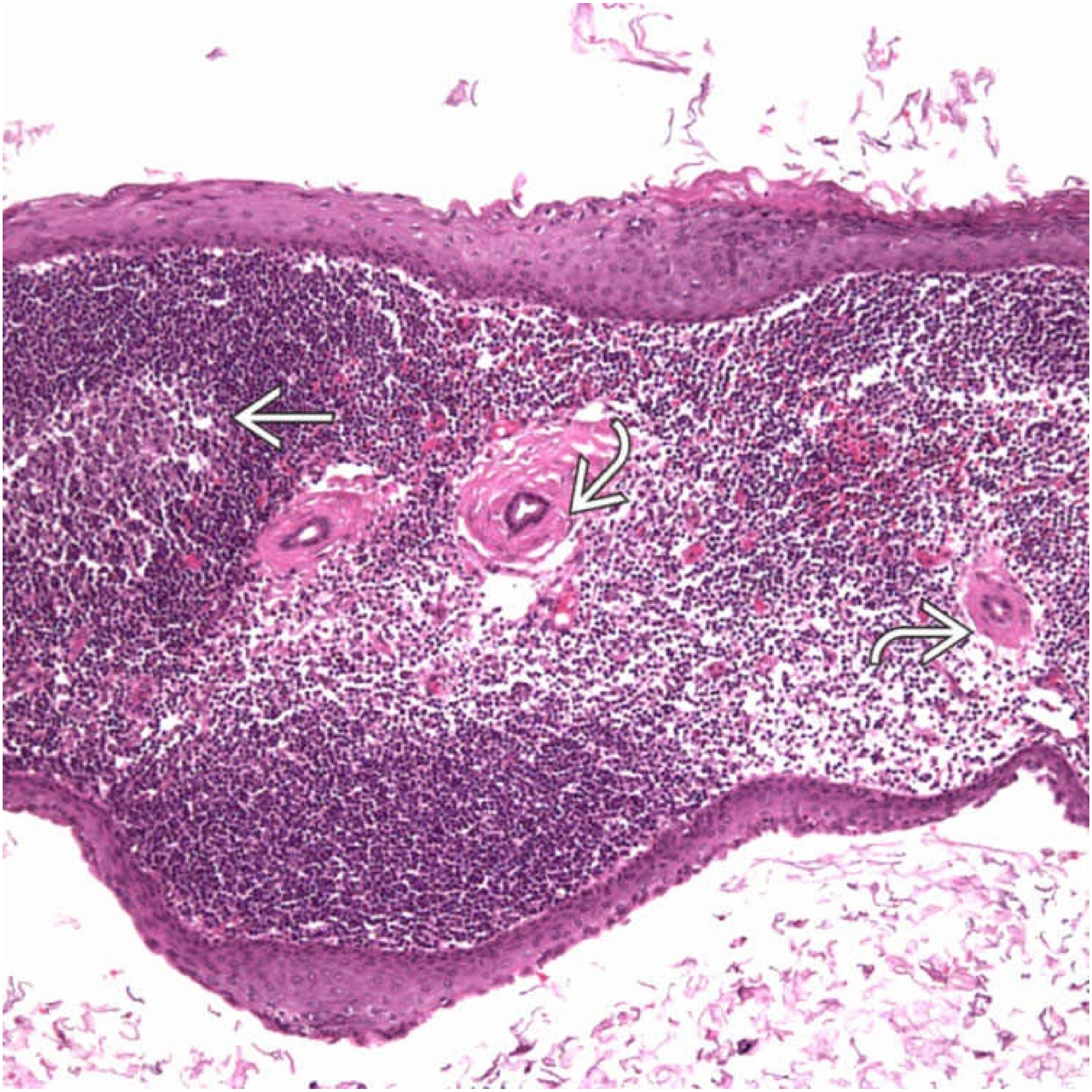


Band-Like Lymphocytic Component

This pancreatic lymphoepithelial cyst shows the prominent band of lymphocytes and overlying keratinizing squamous epithelium . Lymphocytes may extend into the underlying pancreatic parenchyma.



Squamous Epithelium Overlying Lymphocytes
High-power view of this lymphoepithelial cyst shows the benign stratified squamous epithelial lining
above the prominent lymphoid stroma .



Germinal Centers and Pancreatic Ducts
Benign pancreatic ducts are seen within the lymphoid component in the wall of a lymphoepithelial cyst. Germinal centers may be present .

TERMINOLOGY

Definitions

- Nonneoplastic cyst with lymphoid and squamous epithelial components

ETIOLOGY/PATHOGENESIS

Uncertain

- Not associated with conditions related to lymphoepithelial cysts of salivary gland

CLINICAL ISSUES

Epidemiology

- Incidence
    - Rare, accounting for 0.5% of pancreatic cystic lesions
- Age
    - Mean: 56 years
    - Range: 38-82 years
- Sex
    - M:F = 4:1

Presentation

- Vague intermittent abdominal pain
- Nausea/vomiting/diarrhea
- Abdominal mass
- Weight loss
- Often asymptomatic and incidentally discovered

Treatment

- Many can be safely treated conservatively
- Resection limited to symptomatic lymphoepithelial cysts or if diagnosis is uncertain

Prognosis

- Resection is curative
- Malignant transformation has not been described

MACROSCOPIC

General Features

- Multilocular (60%) or unilocular (40%) cystic lesion occurring anywhere in pancreas
    - Cyst contents
    - Smooth or finely granular lining
    - Serous to cheesy/caseous contents
- If lymphoid tissue is prominent, may see band of soft tan tissue surrounding cyst wall

Size

- 1.5-17 cm

MICROSCOPIC

Histologic Features

- Cyst lining
  - Usually stratified squamous epithelium
  - – May show keratinization
- Cuboidal or transitional-like epithelium may be present
- Sebaceous and mucinous goblet cells are rarely seen
- Inflammation, reactive epithelial changes variably present
- Cyst wall &/or trabeculae
  - 1-3 mm in thickness
  - Dense, distinct band of lymphoid tissue composed of mature T cells
    - – Intervening germinal center formation by B cells
- Other elements variably present
  - Epithelioid granulomas
  - Foamy histiocytes
  - Fat necrosis
  - Cholesterol clefts
  - Stromal hyalinization
- Adjacent pancreas is often unremarkable
- Some appear to have arisen in peripancreatic lymph node

DIFFERENTIAL DIAGNOSIS

Epidermoid Cyst of Intrapancreatic Accessory Spleen or Heterotopic Spleen

- Occurs exclusively in tail of pancreas
  - Similarly lined by stratified squamous epithelium, which may be attenuated
  - Surrounded by normal-appearing splenic tissue
  - Varying amounts of red and white pulp, latter may be sparse

Dermoid Cyst

- Difficult to distinguish if composed predominantly of epidermal elements
  - Presence of dermal appendages or hair shafts
  - – Sebaceous glands or hair follicles

Squamoid Cyst of Pancreatic Duct

- Relatively small, unilocular cyst lined by squamous or transitional epithelium without keratinization

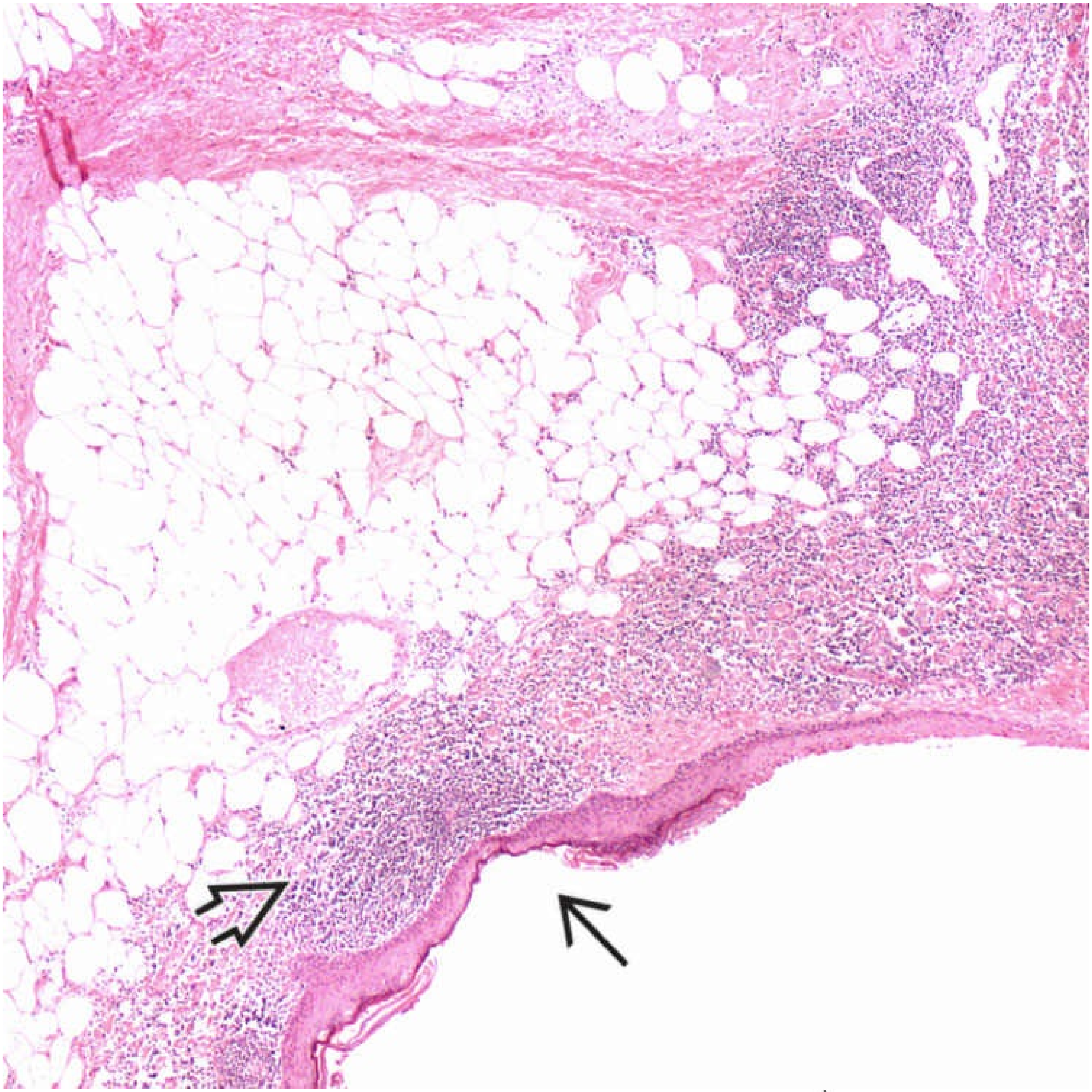
- Often cystically dilated duct
- Surrounded by acinar tissue
- Lumen may contain acidophilic secretions that form concretions

Lymphangioma

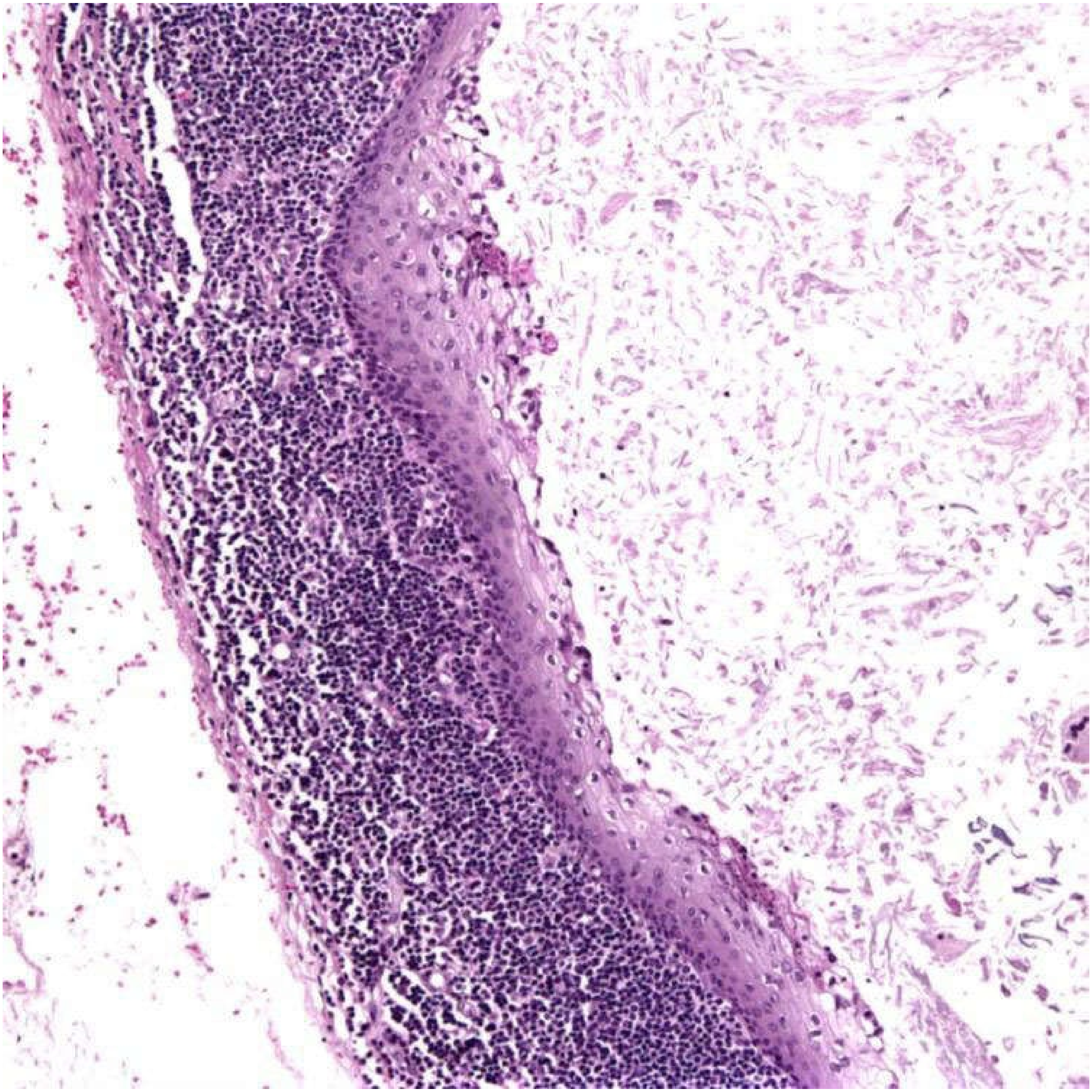
- Multilocular cyst with endothelial lining
- Aggregates of lymphoid tissue rather than thick band of lymphoid tissue

Pseudocyst

- No epithelial lining
  - Sample entire cyst wall before rendering this diagnosis



This cystic lesion of the pancreas is lined by stratified squamous epithelium → and cuffed by a subepithelial band ⇨ of lymphocytes in an example of lymphoepithelial cyst.



High-power view shows an outer band-like rim of lymphocytes, the squamous epithelial lining, and keratinaceous debris in the lumen of the cyst.

SELECTED REFERENCES

1.Okun, SD, et al. Non-neoplastic pancreatic lesions that may mimic malignancy. *Semin Diagn Pathol*. 2016; 33(1):31–42.

3. Mege, D, et al. Lymphoepithelial cyst of the pancreas: an analysis of 117 patients. *Pancreas*. 2014; 43(7):987–995.

4. Basturk, O, et al. Pancreatic cysts: pathologic classification, differential diagnosis, and clinical implications. *Arch Pathol Lab Med*. 2009; 133(3):423–438.

8. Truong, LD, et al. Lymphoepithelial cyst of the pancreas. *Am J Surg Pathol*. 1987; 11(11):899–903.

2. Martin, J, et al. Lymphoepithelial cysts of the pancreas:a management dilemma. *Hepatobiliary Pancreat Dis Int*. 2014; 13(5):539–544.
5. Fukunaga, N, et al. Lymphoepithelial cyst of the pancreas that was difficult to distinguish from branch duct-type intraductal papillary mucinous neoplasm: report of a case. *Surg Today*. 2009; 39(10):901–904.
6. Adsay, NV, et al. Lymphoepithelial cysts of the pancreas: a report of 12 cases and a review of the literature. *Mod Pathol*. 2002; 15(5):492–501.
7. Adsay, NV, et al. Squamous-lined cysts of the pancreas: lymphoepithelial cysts, dermoid cysts (teratomas), and accessory-splenic epidermoid cysts. *Semin Diagn Pathol*. 2000; 17(1):56–65.

SECTION 4
TUMORS OF THE GALLBLADDER AND EXTRAHEPATIC BILIARY TREE

OUTLINE

Intracholecystic Papillary-Tubular Neoplasms

KEY FACTS

Terminology

- Exophytic, noninvasive neoplastic epithelial lesion of gallbladder and biliary tree
  - Includes neoplastic lesions previously classified as adenomas (both intestinal and pyloric types), papillary carcinoma in situ, papillomatosis

Clinical Issues

- Many patients asymptomatic, and ICPN discovered incidentally at cholecystectomy
- Associated with invasive carcinoma in 50% of cases at diagnosis
- 5-year survival of 60% for cases with associated invasive carcinoma, 78% for noninvasive lesions

Macroscopic

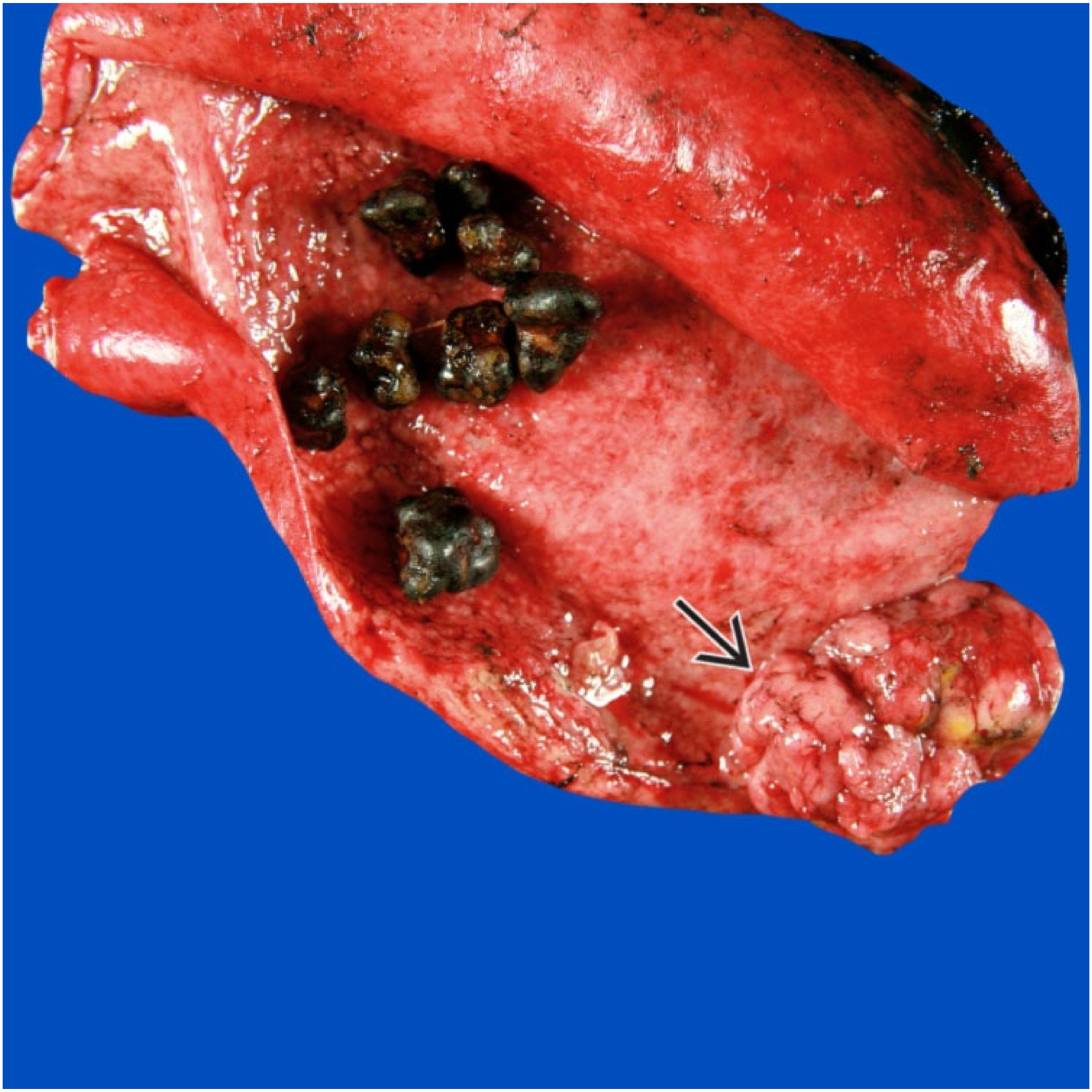
- Most cases are solitary; 1/3 multiple
- May become detached from lumen and grossly mimic gallstones or biliary sludge
- Average size: ~ 2 cm; reported as large as 7 cm

Microscopic

- Classified as tubular (> 75%), papillary (> 75%), or tubulopapillary (25-75% each pattern)
  - Cell types: Gastric (pyloric, foveolar), intestinal, biliary, oncocytic
  - Pyloric type has lowest association with high-grade dysplasia and carcinoma (~ 15%)
  - Intestinal type resembles colonic adenomas
  - Biliary type accounts for ~ 50% of ICPN, frequently associated with high-grade dysplasia and carcinoma

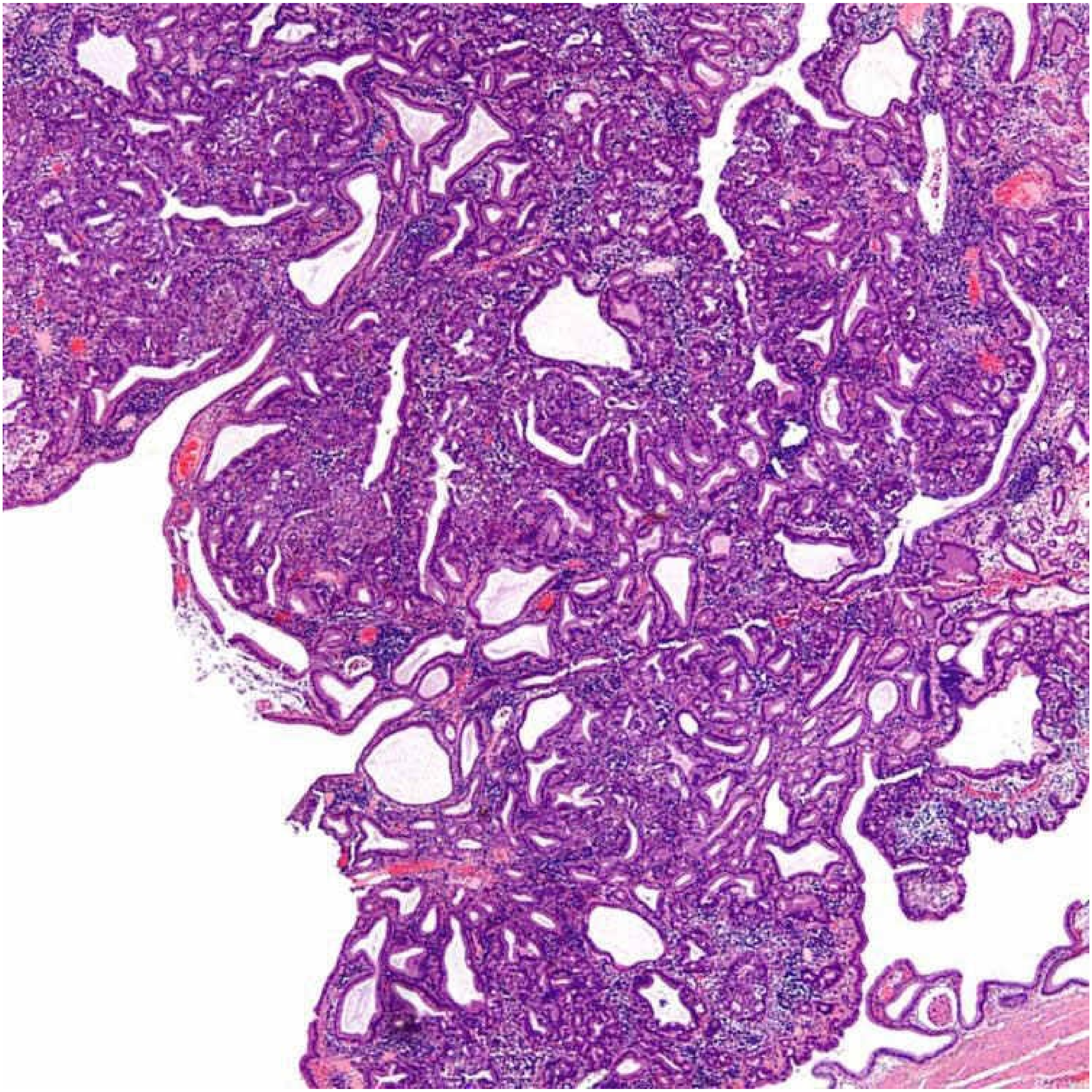
Diagnostic Checklist

- Entire lesion should be submitted for microscopic examination to rule out associated invasive carcinoma

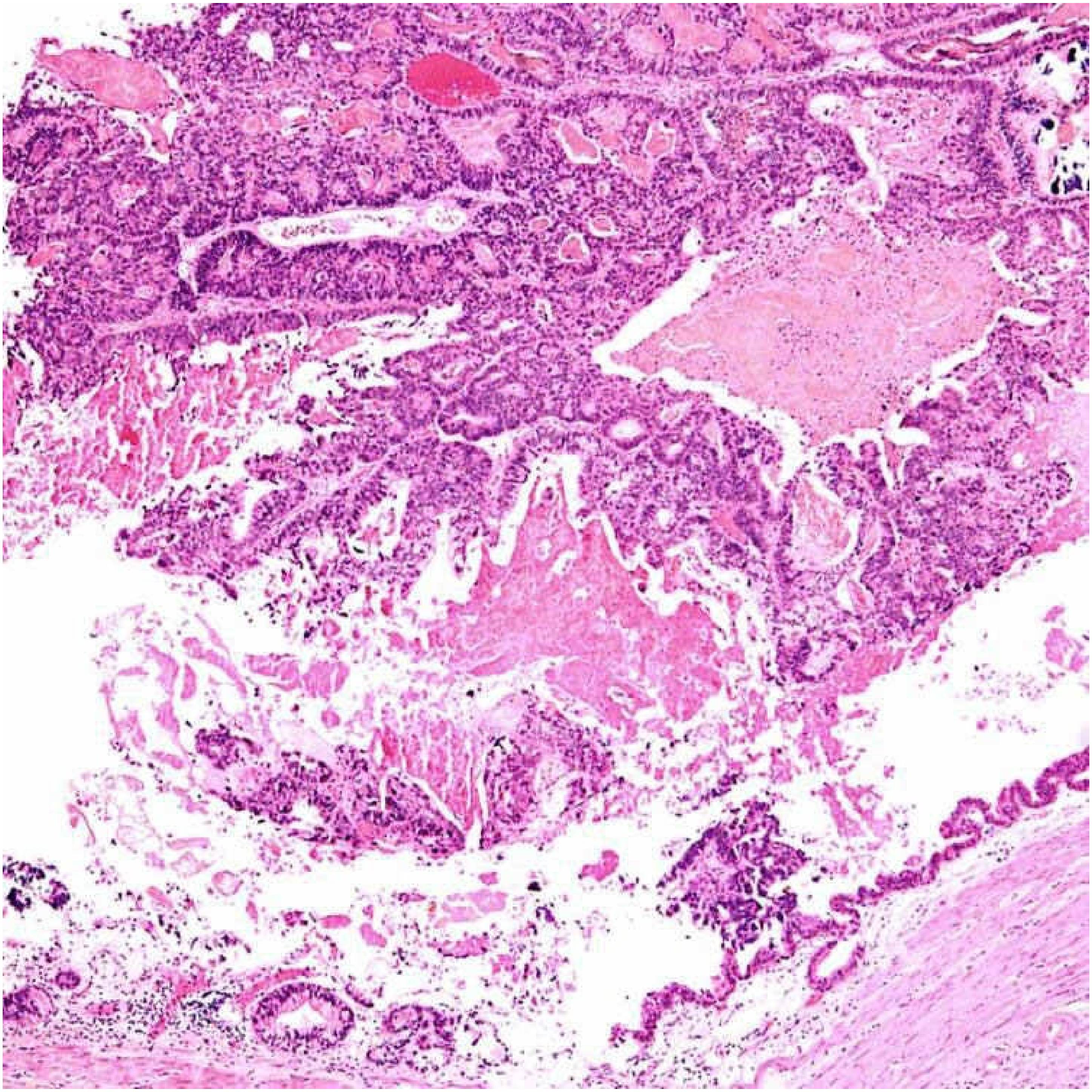


Gallbladder ICPN

An exophytic, lobulated intraluminal polypoid intracholecystic papillary neoplasm → is present in this cholecystectomy specimen, associated with chronic cholecystitis and gallstones.

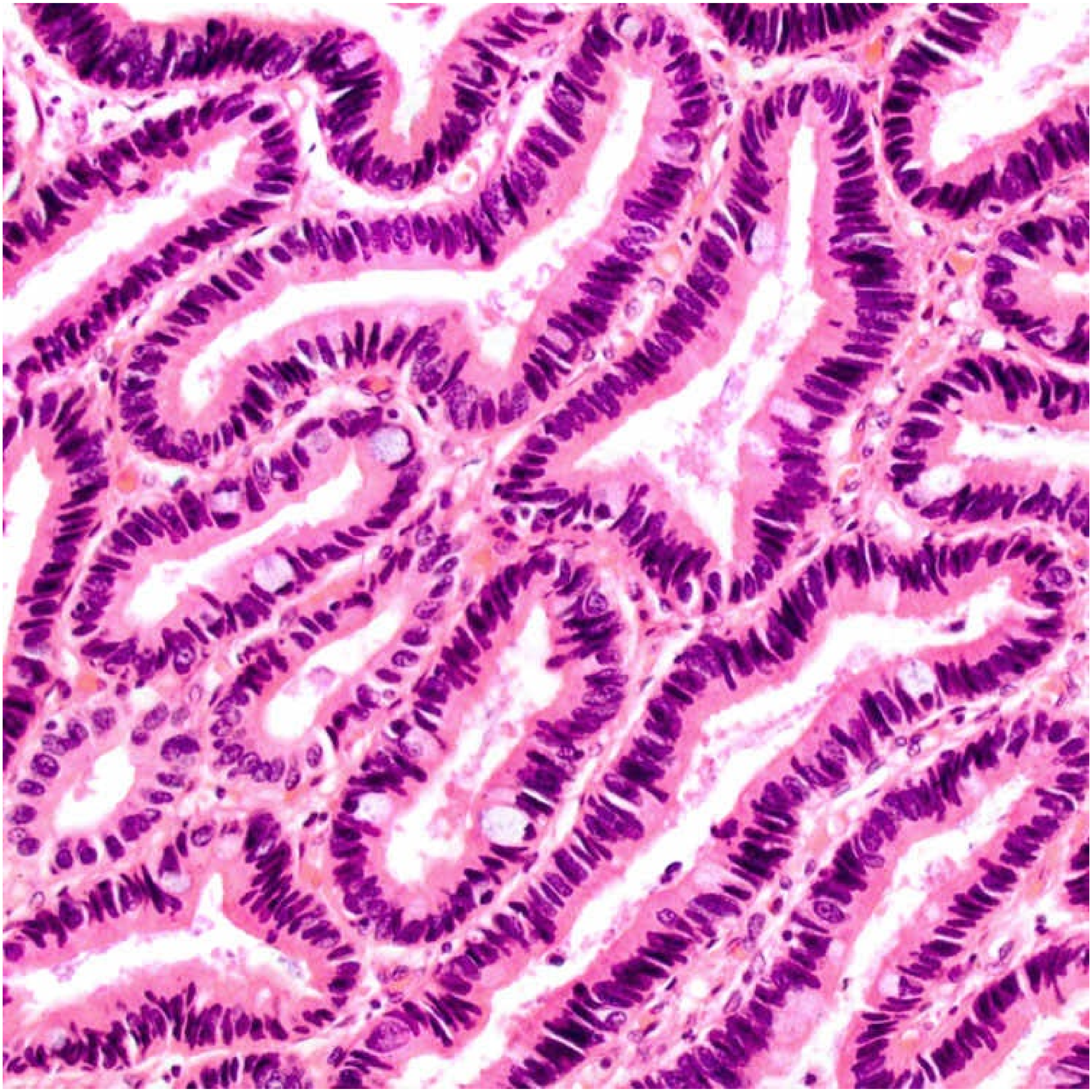


Pyloric Type
This large pyloric-type ICPN forms a polypoid lesion in the lumen of the gallbladder. It is composed of tightly packed pyloric-type glands and tubules.



Detached ICPN

Pedunculated ICPNs often become detached, as shown here, and may resemble biliary sludge or soft stones in the lumen of the gallbladder. This intestinal-type ICPN had high-grade dysplasia.



Intestinal Type
This intestinal-type ICPN shows low-grade dysplasia, similar to a colonic adenoma. Scattered goblet cells are present.

TERMINOLOGY

Abbreviations

- Intracholecystic papillary-tubular neoplasms (ICPN)

Synonyms

- Tumoral intraepithelial neoplasms

Definitions

- Exophytic or polypoid neoplastic epithelial proliferation in gallbladder
  - Includes neoplastic lesions previously classified as adenomas (both intestinal and pyloric types), papillary carcinoma in situ, papillomatosis
  - ≥ 1 cm
  - "Incipient ICPN" has been suggested for adenomas that have dysplasia but are < 1 cm
- Biliary, foveolar, pyloric, intestinal, and oncocytic cell types
- Noninvasive by definition
- Distinct from adjacent mucosa

CLINICAL ISSUES

Epidemiology

- Age
  - Mean: 61 years
- Sex
  - Female predominance (F:M = 2:1)
- Ethnicity
  - More common in Asia

Presentation

- Often discovered incidentally at cholecystectomy
  - When symptomatic, patients typically present with right upper quadrant pain
  - Jaundice, biliary obstruction can occur with multiple lesions or location near neck of gallbladder
- Only ~ 20% of cases associated with gallstones
- ~ 20% of patients have other neoplasms at time of diagnosis
  - Most commonly GI tract and pancreatic tumors

Treatment

- Surgical approaches
  - Cholecystectomy is curative in most cases with noninvasive lesions
  - New primary lesions may subsequently develop in biliary tree

Prognosis

- Invasive carcinoma present in > 50% of cases at diagnosis
  - High-risk features
    - Extent of high-grade dysplasia
    - Extent of papillary component
    - Size of lesion
    - Intestinal or pancreatobiliary phenotype

- Most commonly pancreaticobiliary type adenocarcinomas
- 5-year survival 60% in ICPN with invasive component
- Only minority of gallbladder adenocarcinomas associated with precursor ICPN, however

• 5-year survival 78% for ICPN without invasion
  - Some of these patients die from invasive carcinoma, which may arise from new lesion, or may have been missed at time of resection

IMAGING

General Features

• Larger lesions may be seen as mucosal irregularities or filling defects
  - Often radiographically interpreted as carcinoma
  - ~ 10% mistaken for sludge or stones and not recognized radiographically

MACROSCOPIC

General Features

• Prominent exophytic growth or friable soft excrescences
  - Most cases are solitary
    – Multiple lesions can occur in ~ 30% of cases
- Sessile and broad based or pedunculated
- May become detached from lumen and grossly mimic gallstones or biliary sludge
- Variably present hemorrhage or necrosis

• Most commonly found in fundus and body
• Average size: ~ 2 cm; reported as large as 7 cm

MICROSCOPIC

Histologic Features

• Designated as tubular (> 75%), papillary (> 75%), or tubulopapillary (25-75% each pattern)
  • 4 cell types
  - Biliary
    – Predominantly papillary growth pattern
    – Accounts for ~ 50% of ICPN
    – Frequent association with high-grade dysplasia and adenocarcinoma (~ 70%)
    – Cuboidal, biliary-type epithelial cells
    – Neutrophilic infiltrates common

○ Gastric
– ∼ 36% of cases
– Predominantly tubular pattern
– Foveolar type
□ Higher association with adenocarcinoma (similar to biliary type)
□ Tall, columnar cells with basal nuclei and apical mucin cap, resembling foveolar gastric mucosa
– Pyloric type (2 histologic forms)
□ Lowest association with adenocarcinoma (∼ 15%)
□ Simple mucinous: Tightly packed, evenly sized, small, and bland pyloric-type glands
□ Complex nonmucinous: Pedunculated multinodular polyps with small, nonmucinous complex variably dilated glands, high N:C ratio, squamoid morules
□ Endocrine cells, Paneth cells, amyloid-like stroma seen in some cases of complex nonmucinous pyloric ICPN
□ Previously designated as pyloric gland adenomas
○ Intestinal type
– < 10% of cases
– Resemble colonic adenoma histologically
– Association with adenocarcinoma in 60%
○ Oncocytic type
– Rarest cell type
– Complex papillary architecture with oncocytic features
– Most closely resemble biliary type
○ Mixed histologic subtypes observed in vast majority of cases
• Dysplasia
  ○ Classified as low or high grade
  ○ Tubulopapillary and papillary patterns show greater extent of high-grade dysplasia
  ○ Range of dysplasia common within same lesion

ANCILLARY TESTS

Immunohistochemistry

- Intestinal type
  - Positive: MUC2 (50%), CDX-2, CK20
  - Negative: MUC6, CK7 (variable)
- Pyloric type
  - Positive: CK7, MUC6, MUC5AC (40%), MUC1 (50-60%)
  - Negative: MUC2
- Foveolar type
  - Positive: MUC5AC, MUC6 (some cases)
  - Negative: MUC1, MUC2
    - MUC1 may be positive in areas of high-grade dysplasia
- Biliary type
  - Positive: CK7, MUC1 (majority but not all), MUC5AC (variable)
  - Negative: MUC6, CK20, CDX-2
- Oncocytic type
  - Similar to biliary

Genetic Testing

- *TP53*, *KRAS*, *p16* mutations virtually absent
  - These mutations common in gallbladder adenocarcinoma and flat dysplasia
  - ~ 30% of biliary-type ICPN with high-grade dysplasia show *TP53* mutations
- Complex pyloric gland phenotype associated with mutations in ß-catenin

DIFFERENTIAL DIAGNOSIS

Intestinal Metaplasia

- May form small nodule but no discrete polypoid lesion

Papillary Hyperplasia

- Diffuse mucosal papillary proliferation lined by biliary-type epithelium
- No discrete polypoid lesion

Invasive Carcinoma Arising in ICPN

- Extension of dysplastic epithelium along Rokitansky-Aschoff sinuses may mimic invasive adenocarcinoma
- Invasive carcinomas show irregularly shaped glands, small infiltrative glands, and high-grade cellular atypia

Nodular Hyperplasia of Pseudopyloric Glands

- Pseudopyloric metaplasia commonly seen in association with chronic cholecystitis
- Pseudopyloric glands may coalesce and produce elevations of gallbladder mucosa, mimicking pyloric

type ICPN
- Continuity with adjacent pseudopyloric metaplasia and poor demarcation help distinguish pseudopyloric metaplasia from ICPN

Ectopic Gastric Mucosa

- Parietal and oxyntic cells are invariably present

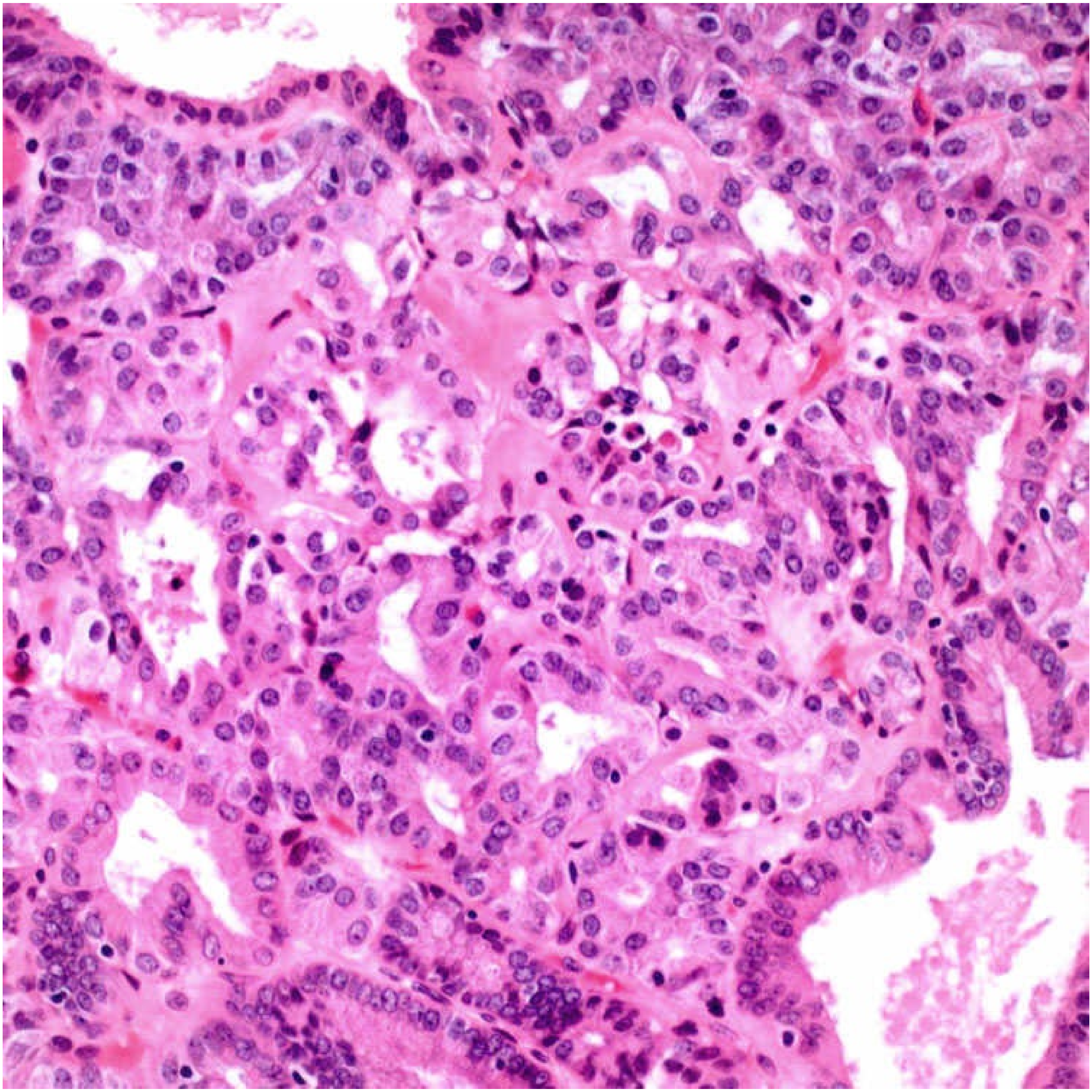
Flat Dysplasia (Intraepithelial Neoplasia)

- Histologic features may overlap with ICPN
- Does not form mass lesion

DIAGNOSTIC CHECKLIST

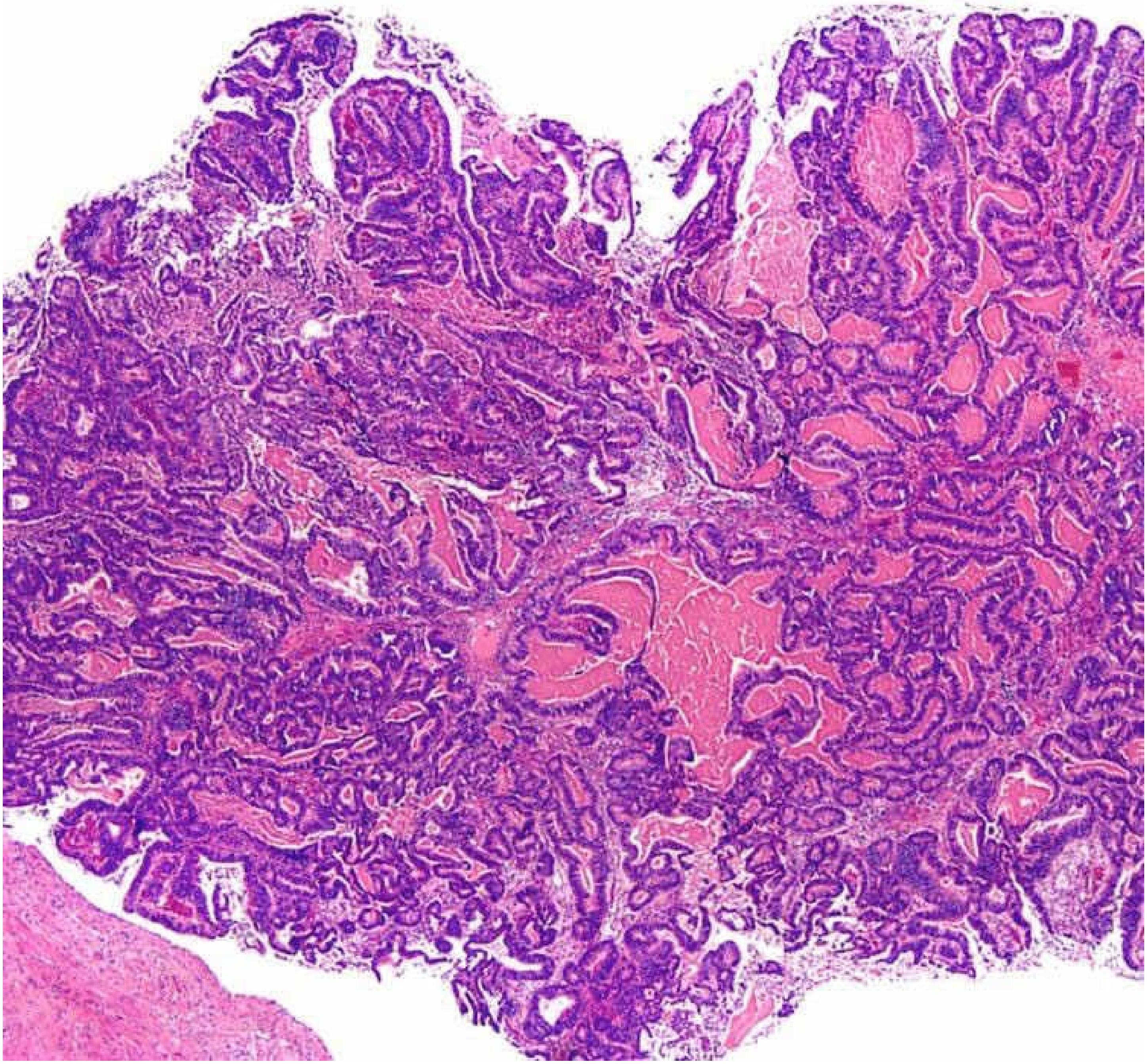
Pathologic Interpretation Pearls

- Entire lesion must be submitted for microscopic examination to rule out associated invasive carcinoma
- Submit any detached fragments in lumen as well

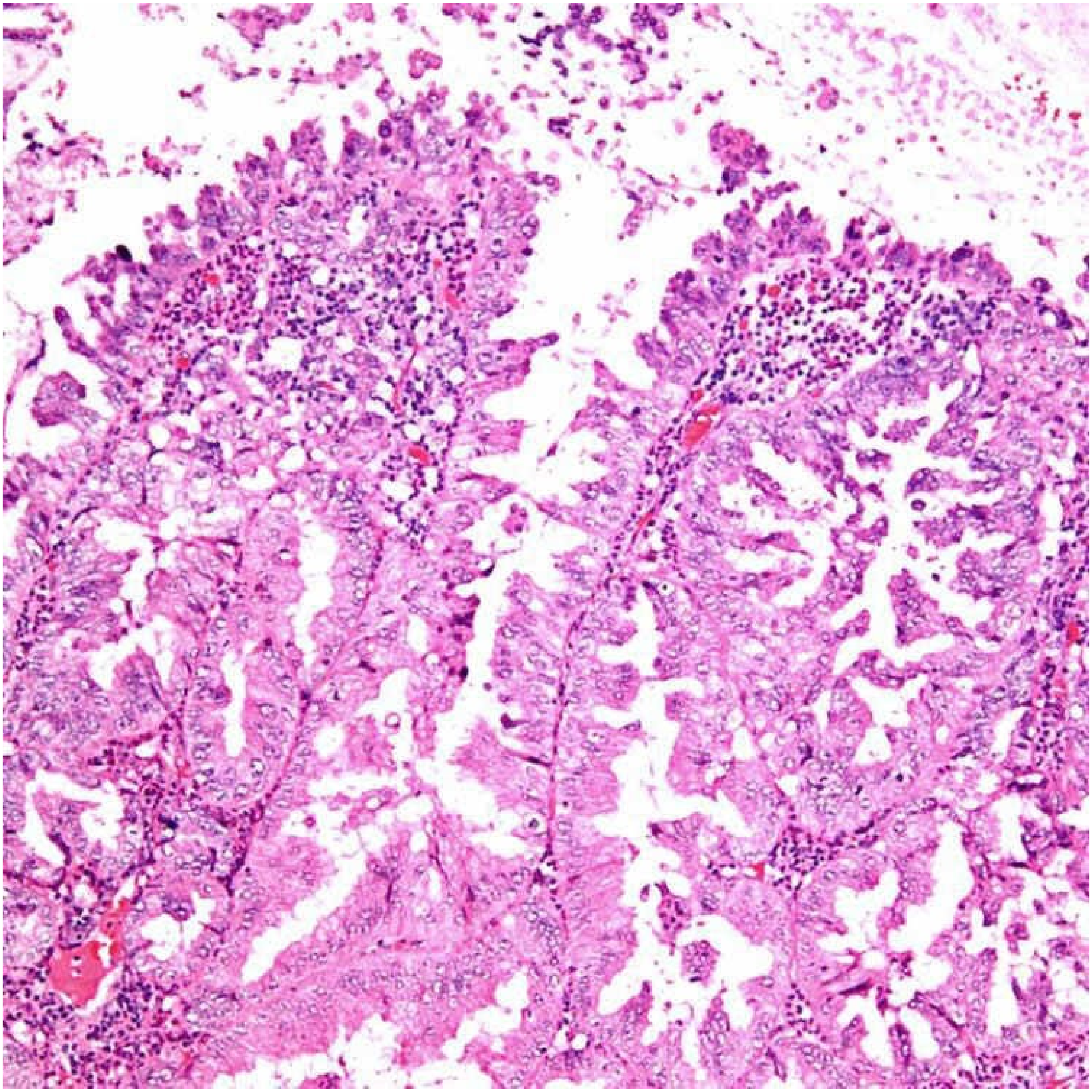


Pyloric Type
Closely spaced glands with little intervening stroma characterize this pyloric-type ICPN. Nuclear atypia is minimal, and nucleoli are inconspicuous. In some cases, complex dilated glands can be seen, often with squamous morules.

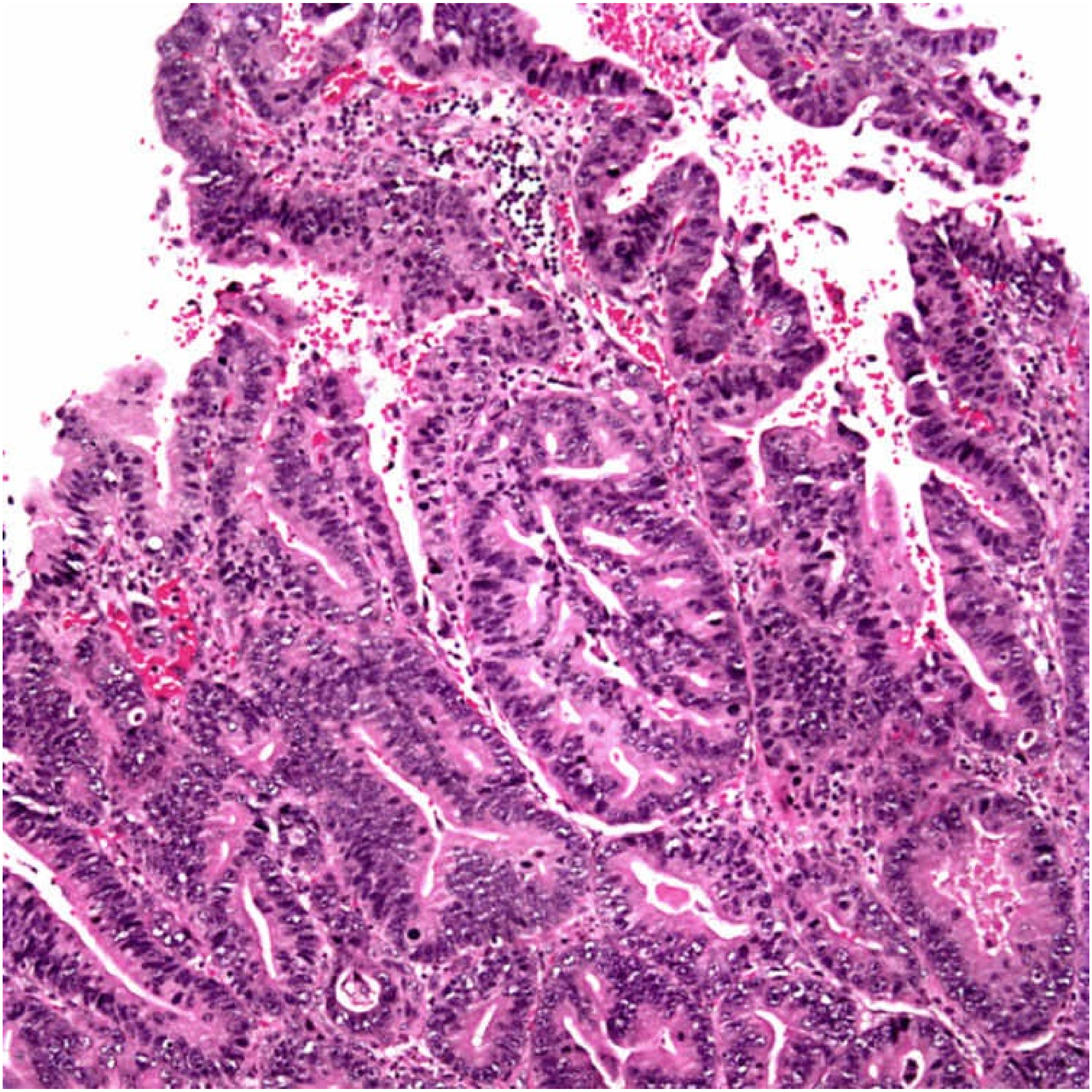
Intestinal Type
This ICPN of the intestinal type contains low-grade dysplasia and resembles a colorectal tubular adenoma.



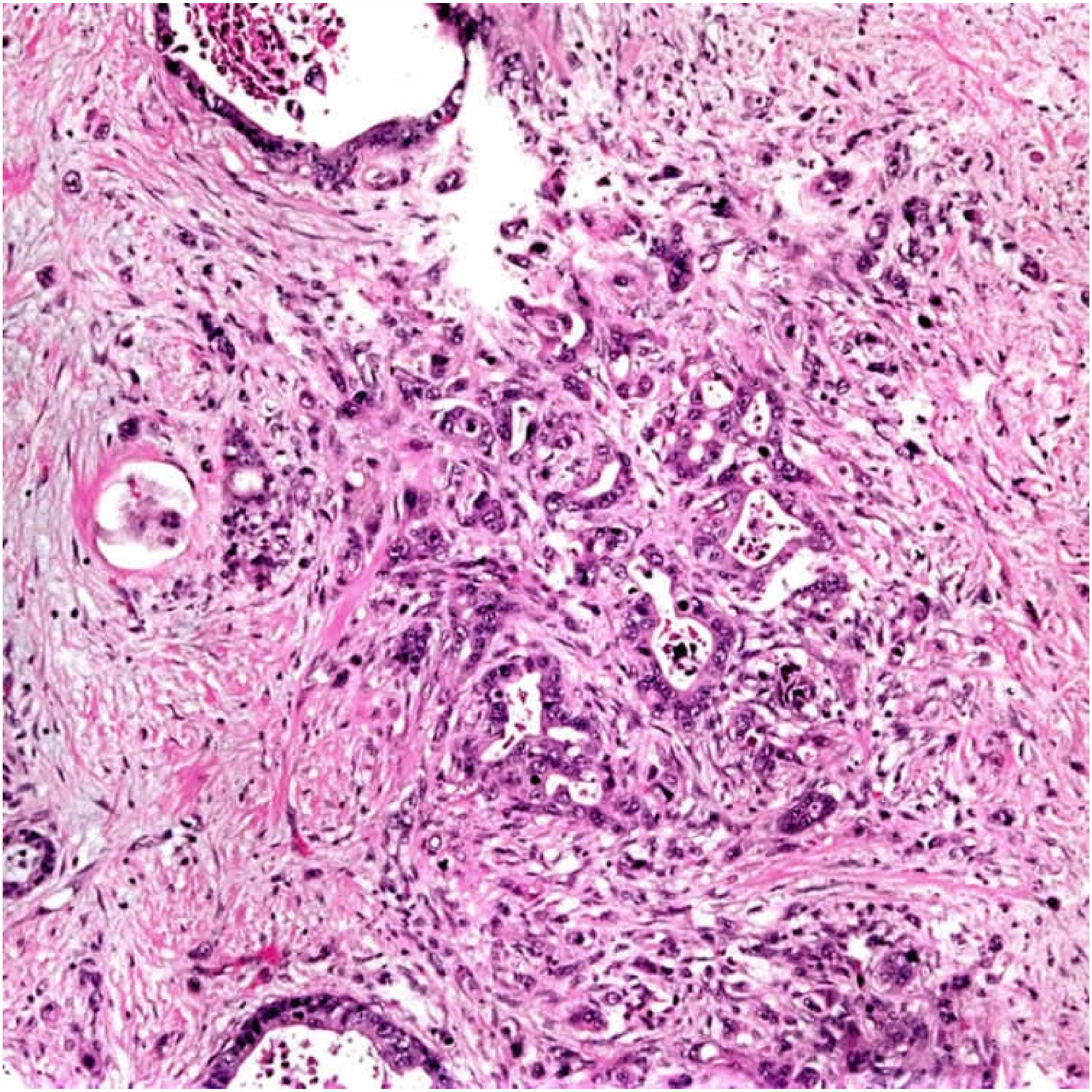
Intestinal Type
This gallbladder contained an incidental detached, polypoid, exophytic intestinal-type ICPN with high-grade dysplasia.



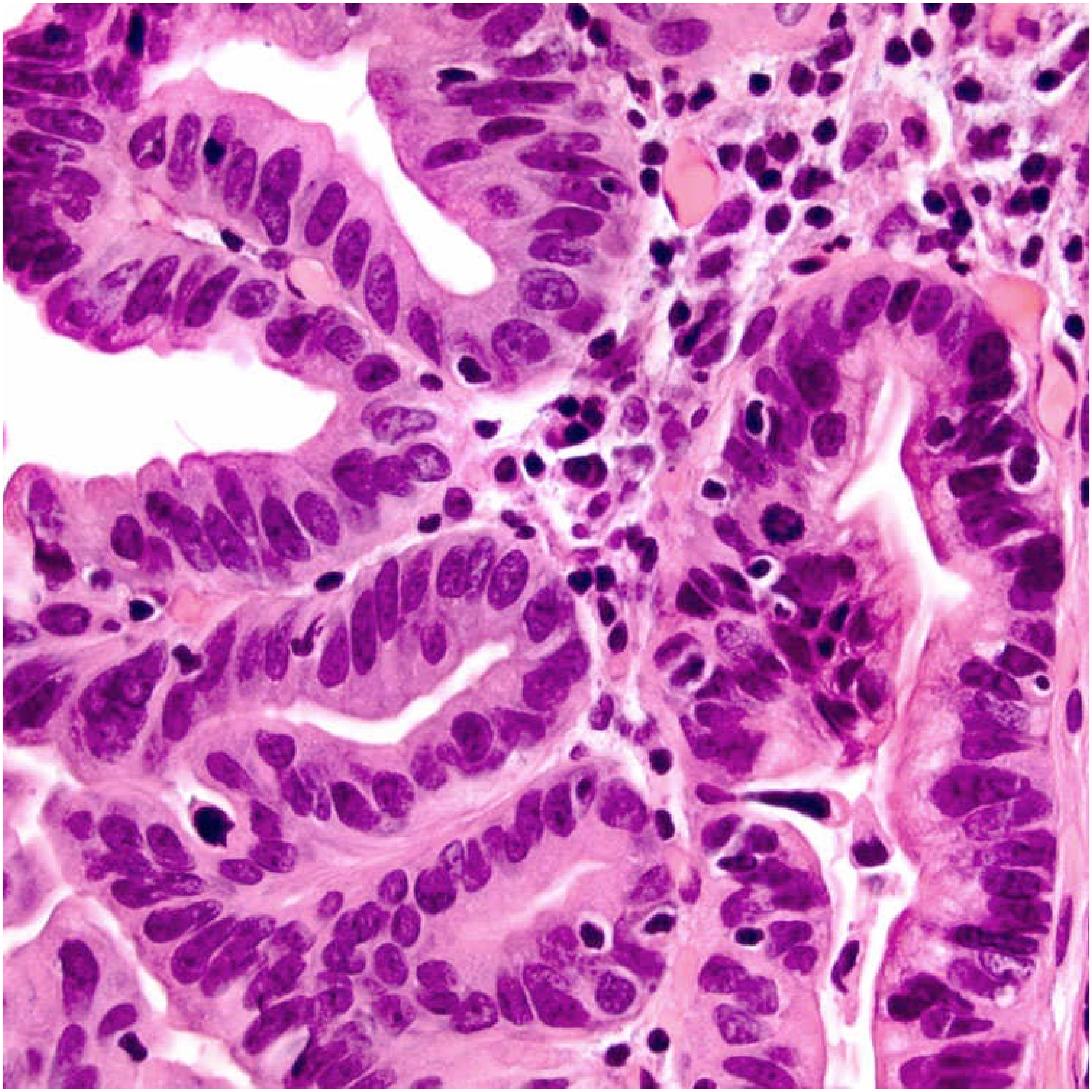
Biliary Type With High-Grade Dysplasia
This biliary-type ICPN contains extensive high-grade dysplasia.



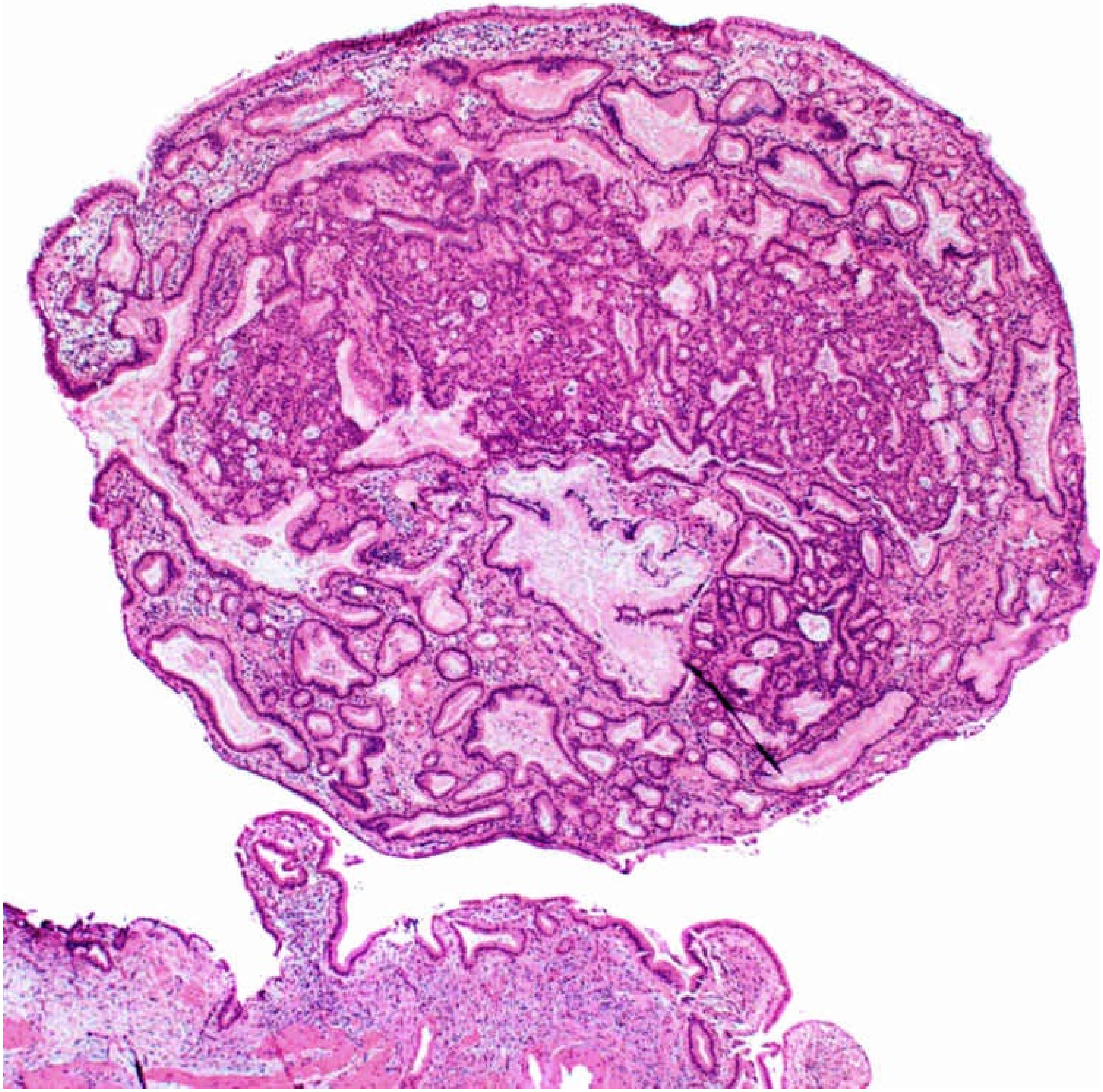
High-Grade Dysplasia
This intracholecystic tubulopapillary neoplasm is composed of tubules and papillary fronds. Cytologic features and cribriform architecture indicate high-grade dysplasia.



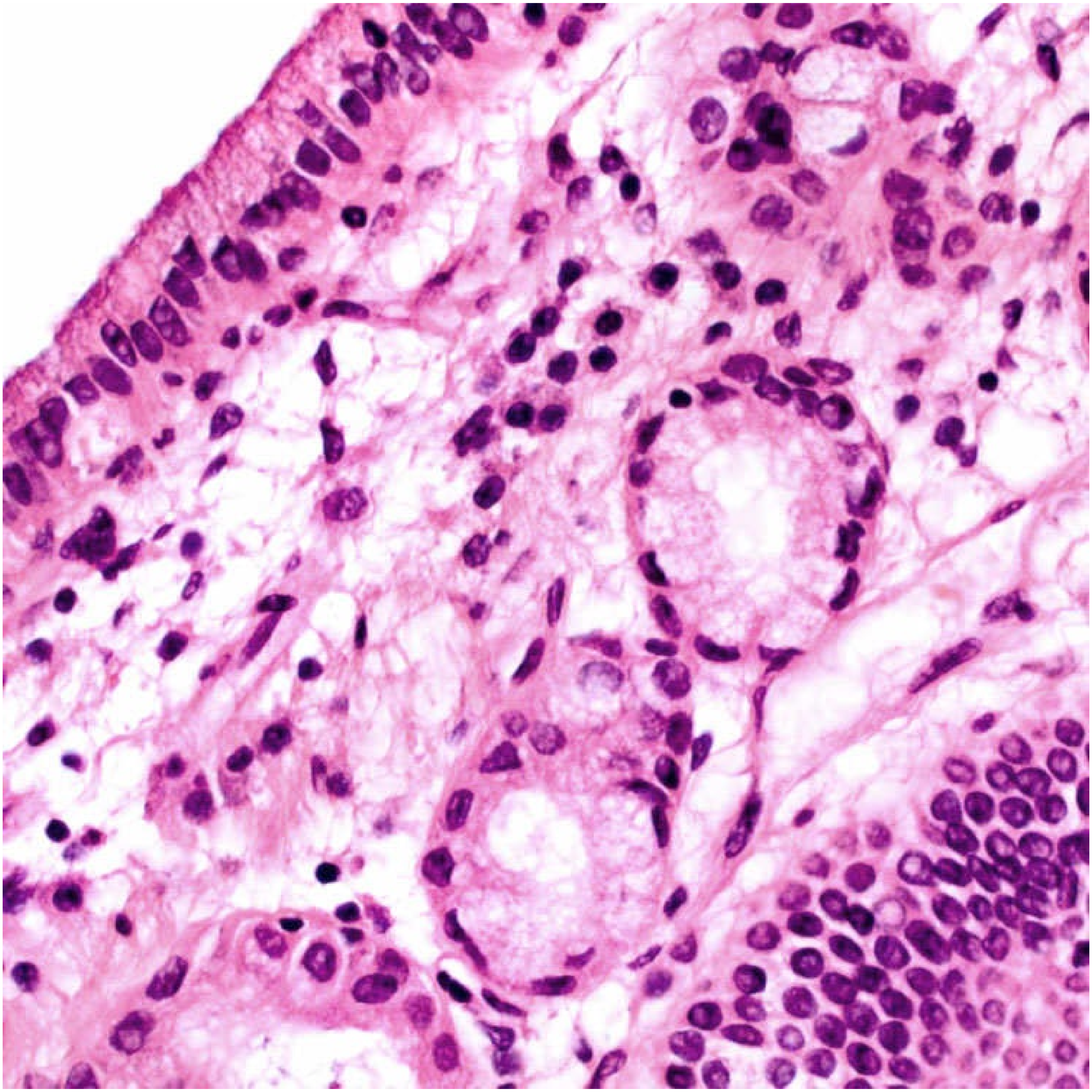
Adenocarcinoma Arising in ICPN
ICPN associated with poorly differentiated invasive adenocarcinoma is shown. The morphologic appearance and prominent desmoplastic reaction indicate a pancreaticobiliary type of adenocarcinoma. Less commonly, mucinous adenocarcinomas can occur in the setting of ICPN.



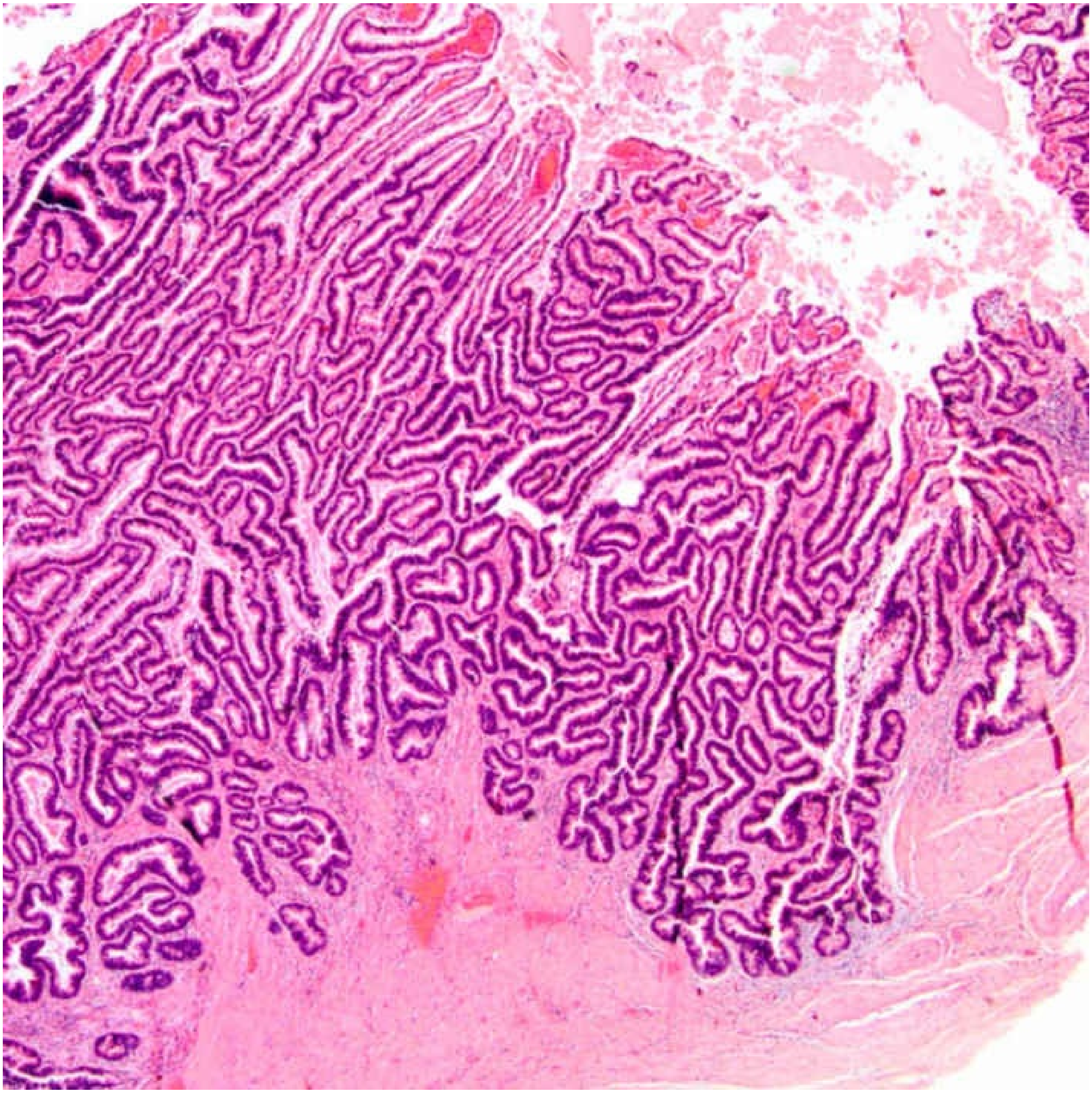
ICPN shows areas of nuclear enlargement, moderate to marked atypia, and loss of polarity indicating high-grade nuclear features of dysplasia.



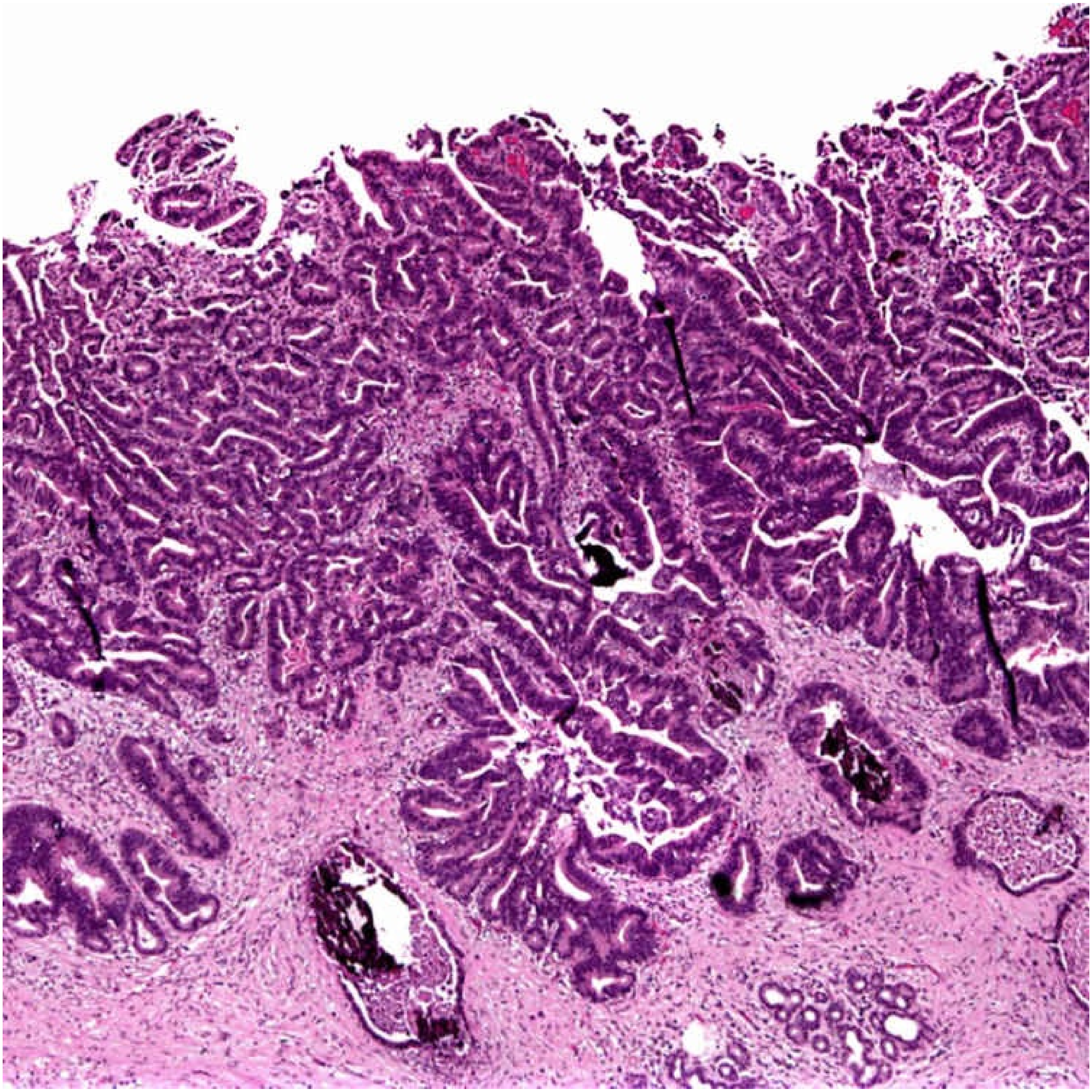
Polypoid lesion is shown in the lumen of the gallbladder. It is composed of tightly packed pyloric-type glands and tubules.



Pyloric-type glands are lined by cells with small, basally located nuclei and pale cytoplasm. Note the absence of apical mucin snouts typical of foveolar epithelium.



This tubulopapillary intestinal-type adenoma is composed of intestinal-type epithelium that resembles an adenoma of the colon.



This patient had multiple ICPNs, which were sessile rather than exophytic, and contained extensive high-grade dysplasia.

SELECTED REFERENCES

1. Adsay, V, et al. Intracholecystic papillary-tubular neoplasms (ICPN) of the gallbladder (neoplastic polyps, adenomas, and papillary neoplasms that are ≥ 1.0 cm): clinicopathologic and immunohistochemical analysis of 123 cases. *Am J Surg Pathol*. 2012; 36(9):1279–1301.
2. Albores-Saavedra, J, et al. Adenomas of the gallbladder. Morphologic features, expression of gastric and intestinal mucins, and incidence of high-grade dysplasia/carcinoma in situ and invasive carcinoma. *Hum Pathol*. 2012; 43(9):1506–1513.
3. Pai, RK, et al. Mutations in the RAS/RAF/MAP kinase pathway commonly occur in gallbladder adenomas but are uncommon in gallbladder adenocarcinomas. *Appl Immunohistochem Mol*

Morphol. 2011; 19(2):133–140.

4. Lee, SH, et al. [Histopathologic analysis of adenoma and adenoma-related lesions of the gallbladder.]. *Korean J Gastroenterol*. 2010; 55(2):119–126.
5. Wani, Y, et al. Aberrant expression of an “intestinal marker” Cdx2 in pyloric gland adenoma of the gallbladder. *Virchows Arch*. 2008; 453(5):521–527.
6. Albores-Saavedra, J, et al. In situ and invasive adenocarcinomas of the gallbladder extending into or arising from Rokitansky-Aschoff sinuses: a clinicopathologic study of 49 cases. *Am J Surg Pathol*. 2004; 28(5):621–628.
7. Abraham, SC, et al. Molecular and immunohistochemical analysis of intraductal papillary neoplasms of the biliary tract. *Hum Pathol*. 2003; 34(9):902–910.
8. Vieth, M, et al. Pyloric gland adenoma: a clinico-pathological analysis of 90 cases. *Virchows Arch*. 2003; 442(4):317–321.
9. Wistuba, II, et al. Gallbladder adenomas have molecular abnormalities different from those present in gallbladder carcinomas. *Hum Pathol*. 1999; 30(1):21–25.
10. Albores-Saavedra, J, et al. Non-neoplastic polypoid lesions and adenomas of the gallbladder. *Pathol Annu*. 1993; 28(Pt 1):145–177.
11. Madden, JJ, Jr., et al. Multiple biliary papillomatosis. *Cancer*. 1974; 34(4):1316–1320.

Adenocarcinoma of Gallbladder

KEY FACTS

Terminology

• Malignant epithelial neoplasm of gallbladder

Etiology/Pathogenesis

• Risk factors
  ○ Chronic inflammation
  – Chronic cholecystitis, cholelithiasis, chronic biliary infections
○ Porcelain gallbladder
○ Primary sclerosing cholangitis
○ Gastrointestinal polyposis

Clinical Issues

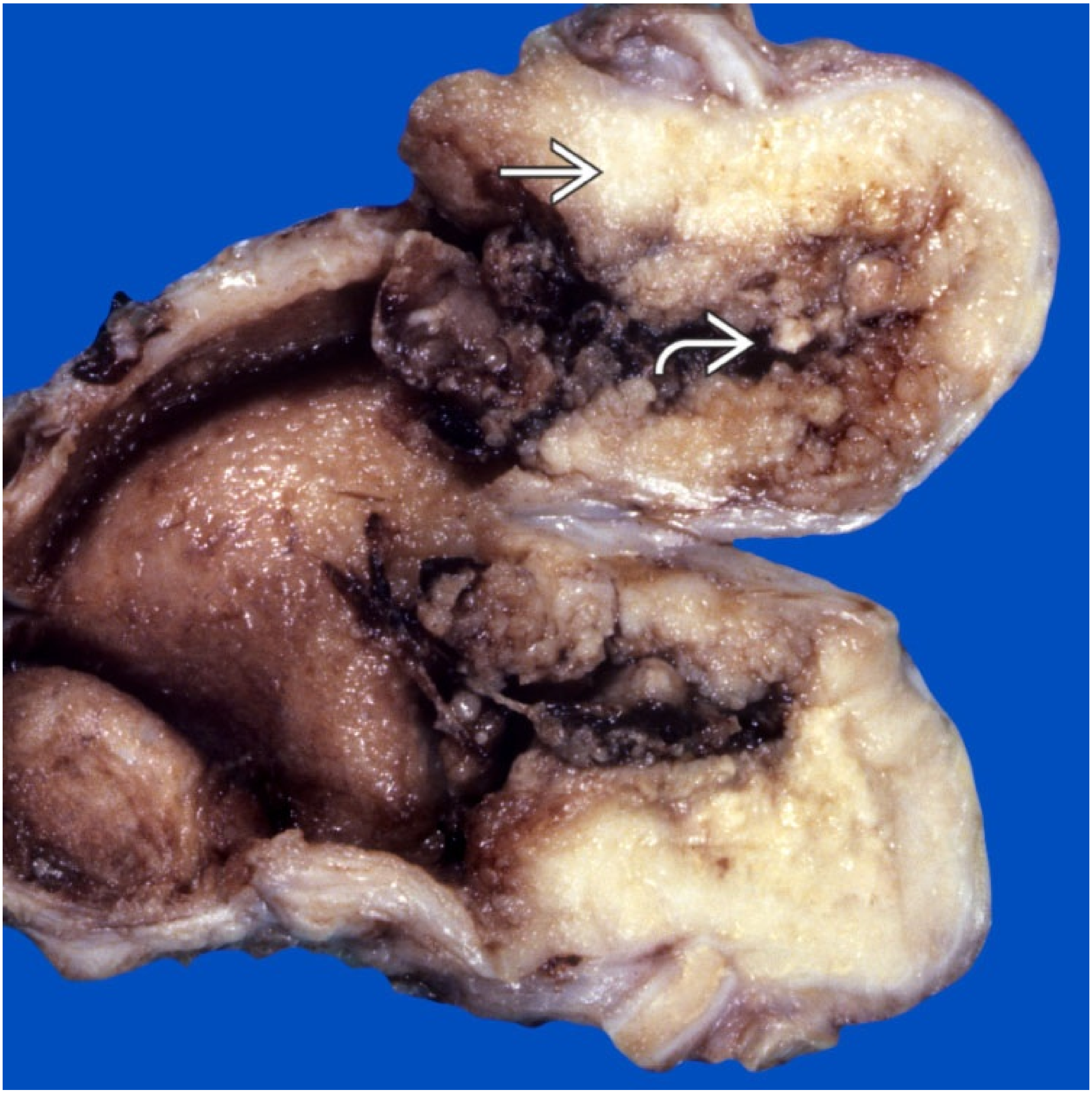
• Most often occurs in India, Chile, Pakistan, and Ecuador
  ○ Females more often affected
• Symptoms often vague, nonspecific
  ○ Often incidental finding at cholecystectomy for cholecystitis or cholelithiasis
• Surgery is most effective and only potentially curative treatment
  ○ Tumor stage probably most important prognostic factor
• Overall 5-year survival ~ 10%

Macroscopic

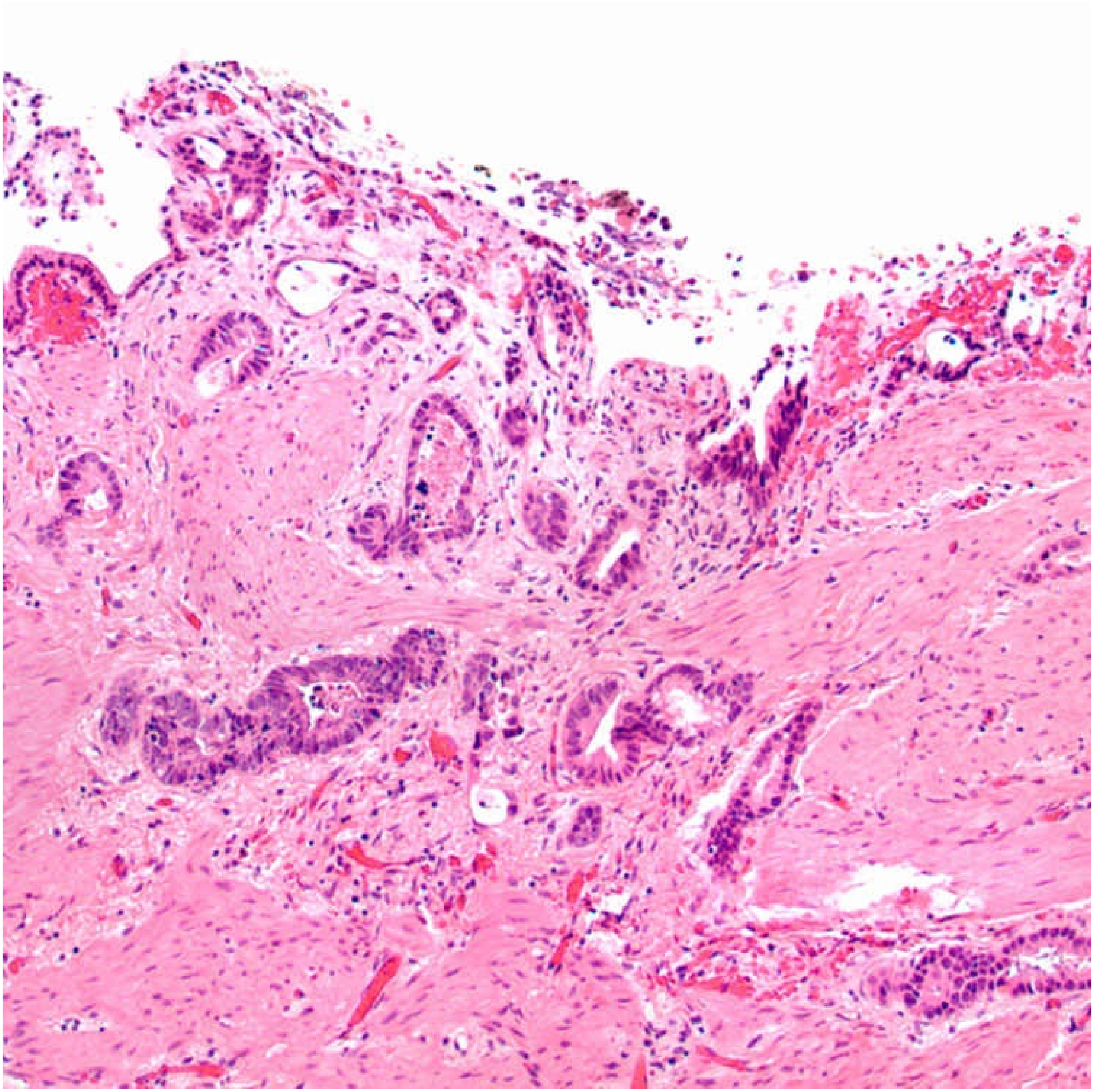
• Area of thickening and induration of gallbladder wall
  ○ Tumor may be difficult to appreciate grossly
• Exophytic or polypoid mucosal mass

Microscopic

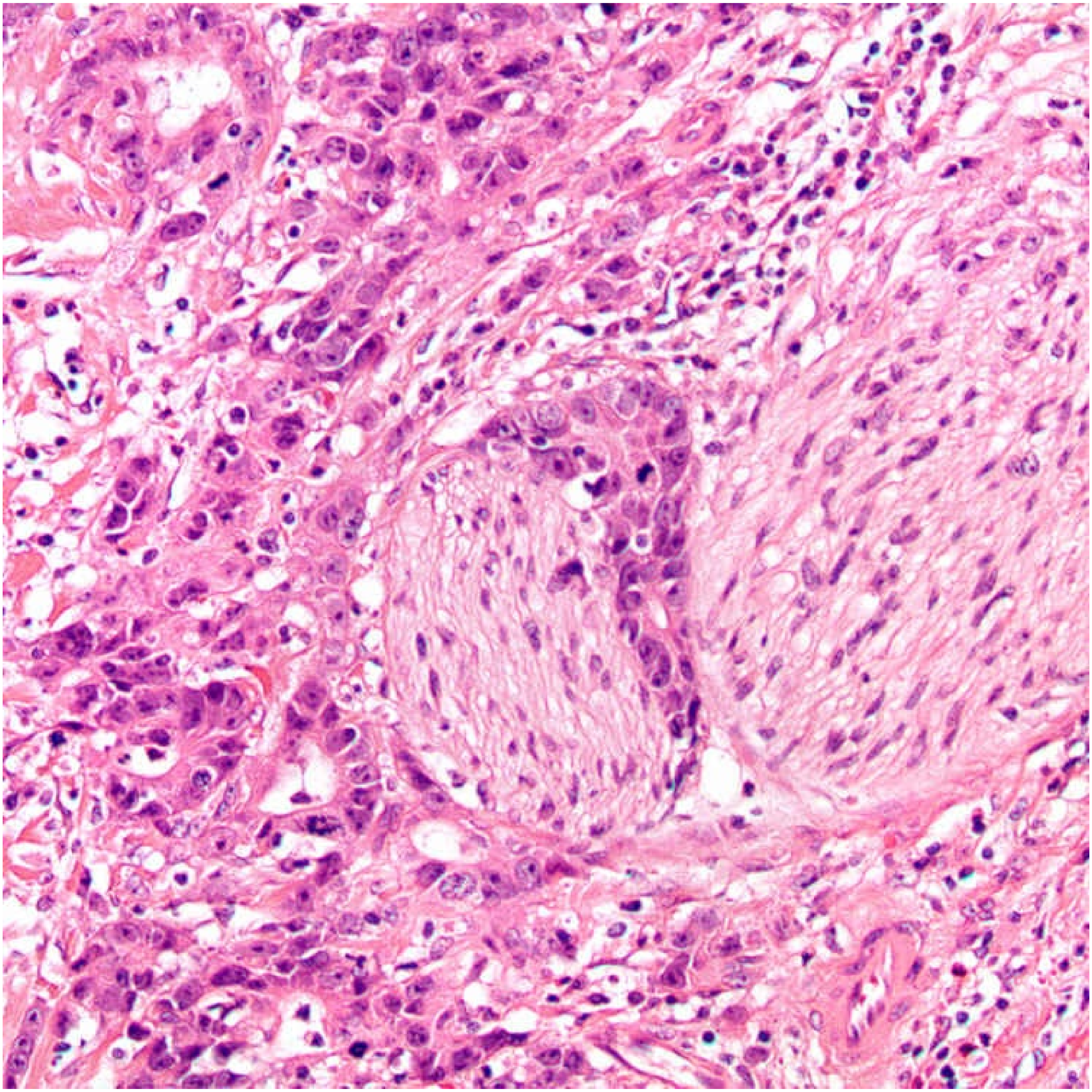
- Malignant glands, clusters, or individual cells invading gallbladder wall
  - Some extremely well-differentiated tumors are deceptively bland and difficult to recognize
  - Multiple histologic variants recognized by WHO
- Majority of cases associated with epithelial dysplasia &/or carcinoma in situ



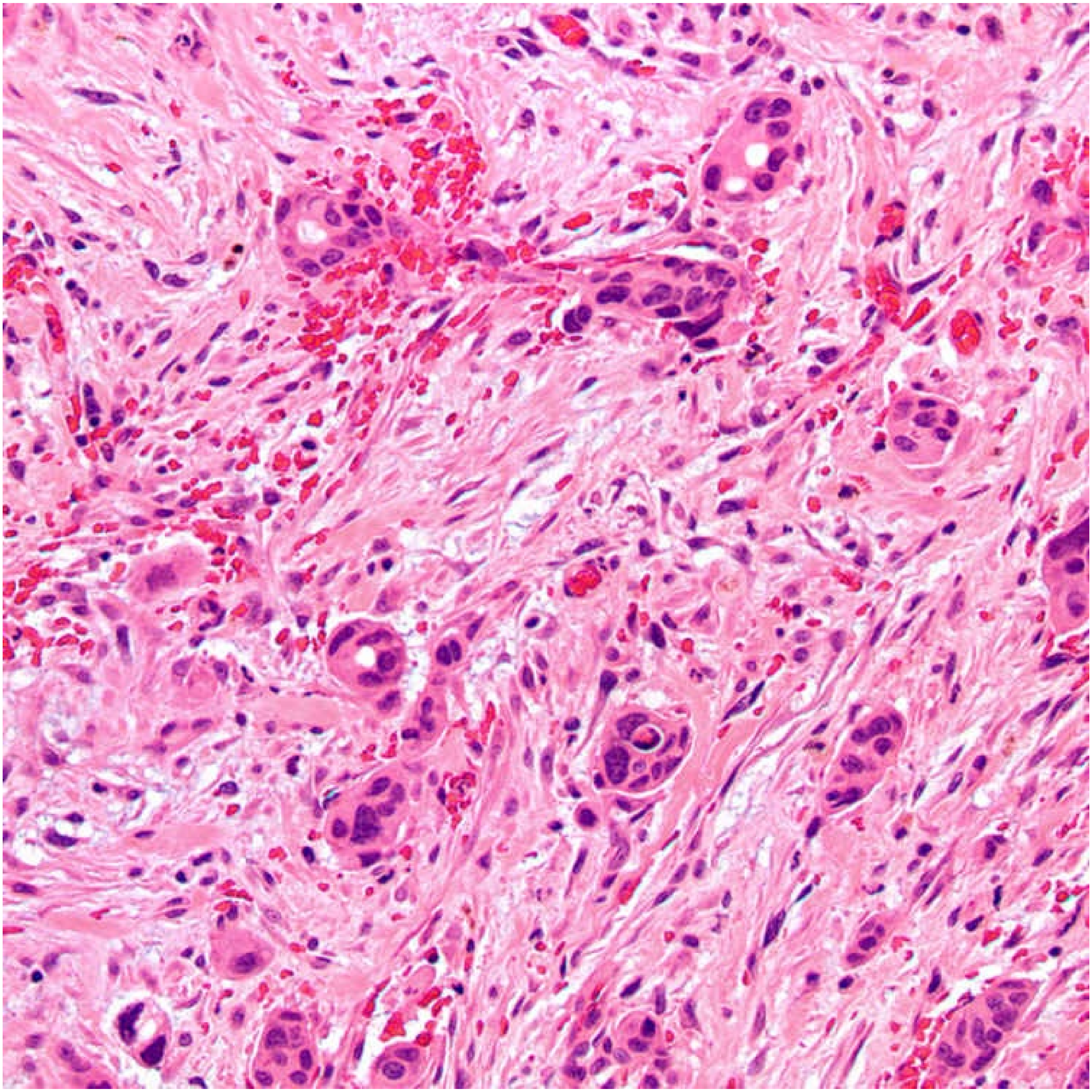
Gallbladder Adenocarcinoma, Gross
This gross cholecystectomy specimen with adenocarcinoma contains areas of mucosal irregularity associated with thickening of the gallbladder wall .



Gallbladder Adenocarcinoma, Low Power
This low-power view of gallbladder adenocarcinoma shows irregular neoplastic glands invading the smooth muscle of the gallbladder wall.



Gallbladder Adenocarcinoma, Perineural Invasion
Perineural invasion is frequently seen in association with gallbladder adenocarcinoma.



Gallbladder Adenocarcinoma, Desmoplasia
Irregular, abortive glands and single cells have associated prominent desmoplastic stroma in this invasive gallbladder adenocarcinoma.

TERMINOLOGY

Definitions

• Malignant glandular epithelial neoplasm of gallbladder

ETIOLOGY/PATHOGENESIS

Risk Factors

- Chronic inflammation
  - Chronic cholecystitis and cholelithiasis
  – > 80% of gallbladder adenocarcinomas are associated with gallstones

- Chronic biliary infections

– *Opisthorchis viverrini*

– *Salmonella typhi*

- Pancreatobiliary reflux

- Porcelain gallbladder
  - > 10% of affected patients have or will develop adenocarcinoma
- Primary sclerosing cholangitis (PSC)
  - Gallbladder adenocarcinoma reported in ~ 14% of patients undergoing liver transplantation for PSC
- Gastrointestinal polyposis
  - Familial adenomatous polyposis coli
  - Gardner syndrome
  - Peutz-Jeghers syndrome

Molecular Alterations

- Reported *KRAS* mutation rates vary from 0-50%
- *TP53* mutations common in late-stage disease

CLINICAL ISSUES

Epidemiology

- Incidence
  - Reported 1.43 cases per 100,000 persons at risk
  - Rates of incidental diagnosis at time of laparoscopic cholecystectomy range from 0.28-2.10%
- Age
  - Predominantly affects elderly patients
  - Mean: 65 years
- Sex
  - Females more often affected (F:M = 3:1)
- Ethnicity
  - Most often occurs in India, Chile, Pakistan, and Ecuador
  - In western countries, Latin American and Native American individuals at greatest risk

Presentation

- Symptoms often vague, nonspecific
  - Upper abdominal pain
  - Weight loss

- Fever
- Jaundice
- Many patients asymptomatic
  - Tumor found incidentally at time of cholecystectomy

Laboratory Tests

- Elevated alkaline phosphatase

Treatment

- Surgery
  - Most effective and only potentially curative treatment
  - – Not effective for advanced disease
- Low-stage tumors
- – Often identified incidentally at time of cholecystectomy for cholelithiasis or cholecystitis
- – Simple cholecystectomy may be adequate therapy
- □ Reexcision of bed of gallbladder may be considered later
- Advanced tumors
- – Radical cholecystectomy with lymphadenectomy and right hepatic lobectomy
- Adjuvant chemotherapy
  - Gemcitabine and gemcitabine-based regimens appear to be most effective to date

Prognosis

- ~ 10% overall 5-year survival
  - 42% 5-year survival for patients with resectable tumors
- Tumor stage probably most important prognostic factor
- Other prognostic factors
  - Tumor grade
    - – Poorly differentiated tumors associated with poor survival
  - Lymph node metastases
  - Completeness of resection

IMAGING

Radiographic Findings

- Various appearances may be seen on imaging
  - Tumor mass occupying or replacing gallbladder lumen

– 40-65% of tumors
- Localized or diffuse wall thickening
- Polypoid lesion in gallbladder lumen
- Liver invasion may be seen

- US is common 1st-line test for suspected gallbladder disease
  - High sensitivity for advanced tumors
  - Unreliable for staging and diagnosis or early tumors
- CT and MR provide more detailed information
  - Tumor staging
  - Evaluate for metastases

MACROSCOPIC

General Features

- Location
  - Fundus (60%), body (30%), or neck (10%) of gallbladder
- Variable gross appearances
  - Area of thickening and induration of gallbladder wall
  - Exophytic or polypoid mucosal mass
- Tumor may not be grossly evident
- Tumors often firm, white, and gritty on cut section

Sections to Be Submitted

- Cystic duct margin
  - Tumors are often incidental and more often located near gallbladder neck
  - Evaluate margin for carcinoma or dysplasia
- Hepatic resection margin
- Gallbladder dysplasia
  - If identified, extensive sampling warranted to exclude occult carcinoma
  - Dysplasia can cause granular mucosal patches but may not be grossly recognizable

MICROSCOPIC

Histologic Features

- Malignant glands, clusters, or individual cells invading gallbladder wall
  - Complex and irregular glands can also be seen
- Wide spectrum of histologic appearances
  - May be extremely well differentiated
    - Some tumors are deceptively bland
    - May exhibit well-formed glands and only minimal cytologic abnormalities
    - Infiltrative growth pattern, nuclear grooves and anisocytosis, and mitotic activity are helpful clues

- Malignant glands/cells may be rare and widely spaced in abundant desmoplastic stroma
- Multiple histologic variants recognized by WHO
  - Papillary adenocarcinoma
  - Intestinal-type or gastric foveolar-type adenocarcinoma
  - Mucinous adenocarcinoma
  - Clear cell adenocarcinoma
  - Signet ring cell carcinoma
  - Adenosquamous carcinoma
  - Micropapillary
  - Adenosquamous carcinoma or squamous cell carcinoma
  - Small cell or large cell neuroendocrine carcinoma
  - Undifferentiated carcinoma
  - Biliary cystadenocarcinoma

- Majority of cases associated with epithelial dysplasia &/or carcinoma in situ
  - Dysplasia or carcinoma in situ are usually incidental findings in cholecystectomy
- Perineural invasion is common

Cytologic Features

- Peritoneal cytology most helpful in patients with advanced tumors

ANCILLARY TESTS

Immunohistochemistry

- Similar to other adenocarcinomas arising in pancreaticobiliary tree
- Most tumors CK7 and CK19 (+) with variable expression of CK20

DIFFERENTIAL DIAGNOSIS

Chronic Cholecystitis

- Rokitansky-Aschoff sinuses (RAS) can mimic invasive adenocarcinoma
  - Usually RAS consist of larger glandular structures that are contiguous with surface epithelium
  - Can extend deeply into and even through gallbladder wall (similar to diverticula)
  - May be surrounded by fibrotic stroma that mimics desmoplastic stroma
- Even more problematic if epithelial dysplasia or carcinoma in situ involves RAS
  - Adenocarcinoma arising in RAS reported but extremely rare
- Adenocarcinoma usually comprised of smaller glands with more cytologic atypia than RAS
- Neoplastic glands are usually smaller and more crowded than RAS

Adenomyoma

• Irregular, dilated cystic structures set in hypertrophic smooth muscle
• Bland epithelium and lobular configuration distinguishes adenomyoma from adenocarcinoma

Acute Cholecystitis

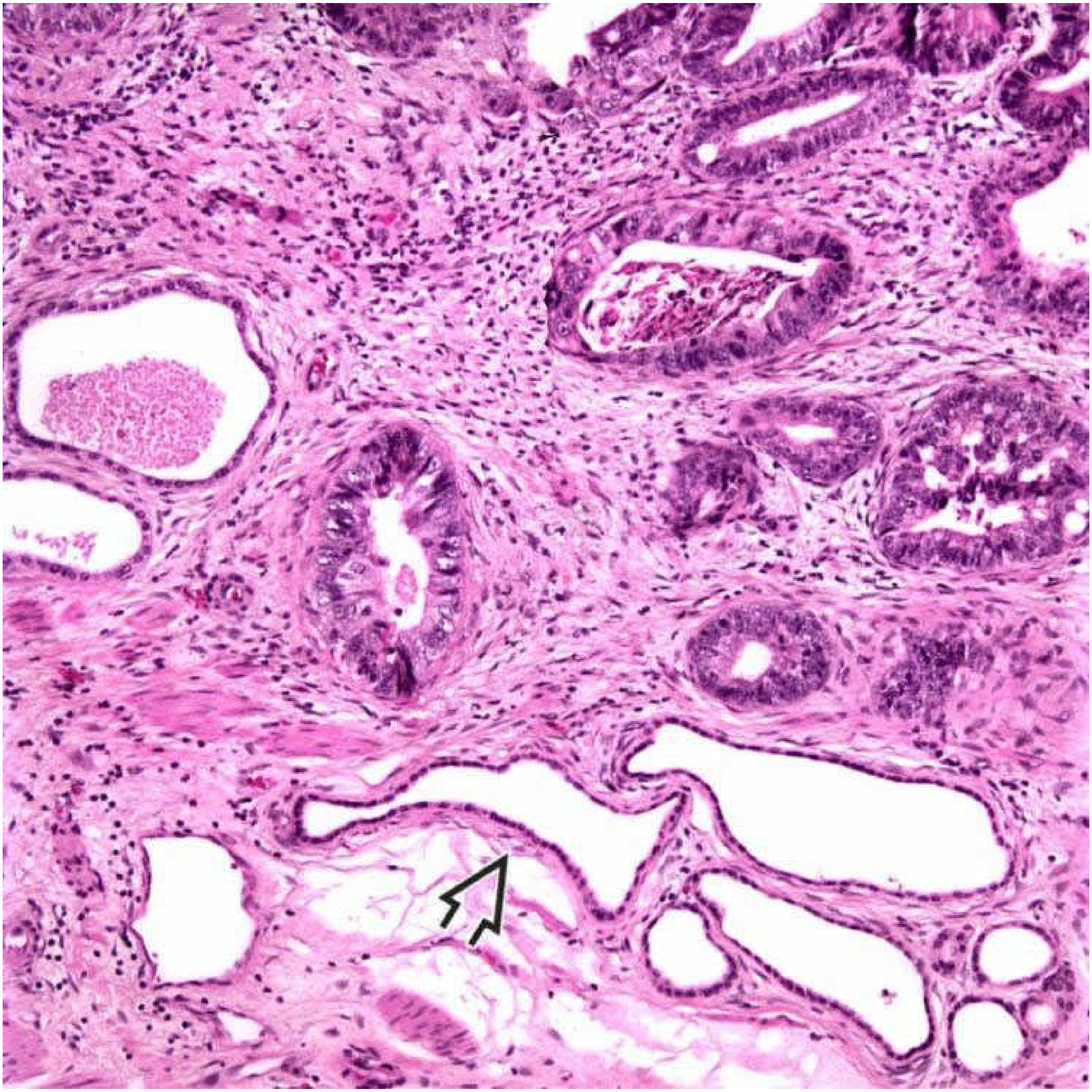
• Reactive epithelial alterations may be mistaken for dysplasia or carcinoma
• Use caution when making diagnosis in setting of marked inflammation

Ducts of Luschka

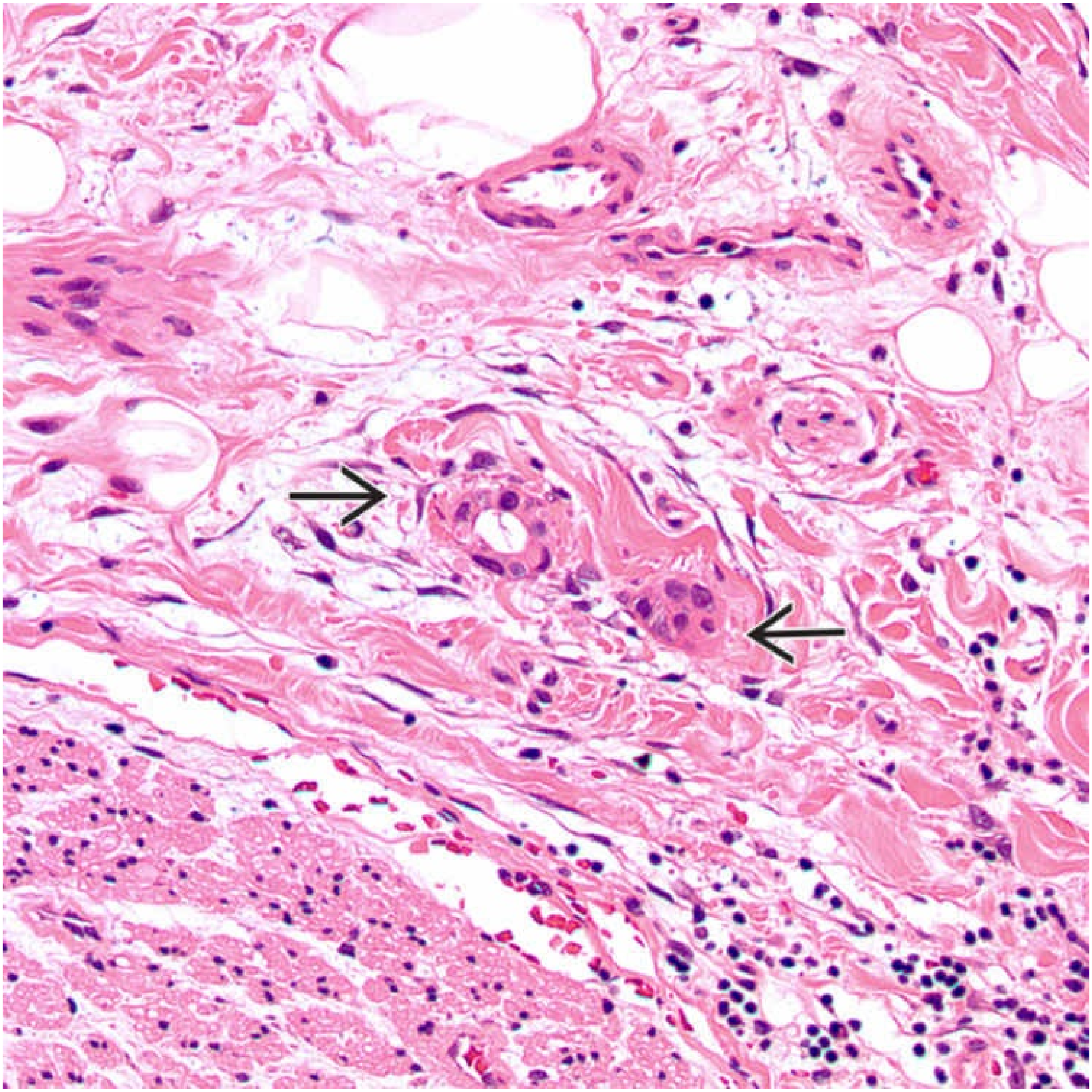
• Groups of small, round, benign ducts often seen at hepatic surface of gallbladder
• Lack invasive growth pattern or cytologic features of malignancy
• May be very challenging to distinguish from adenocarcinoma on frozen section

Metastatic Adenocarcinoma to Gallbladder

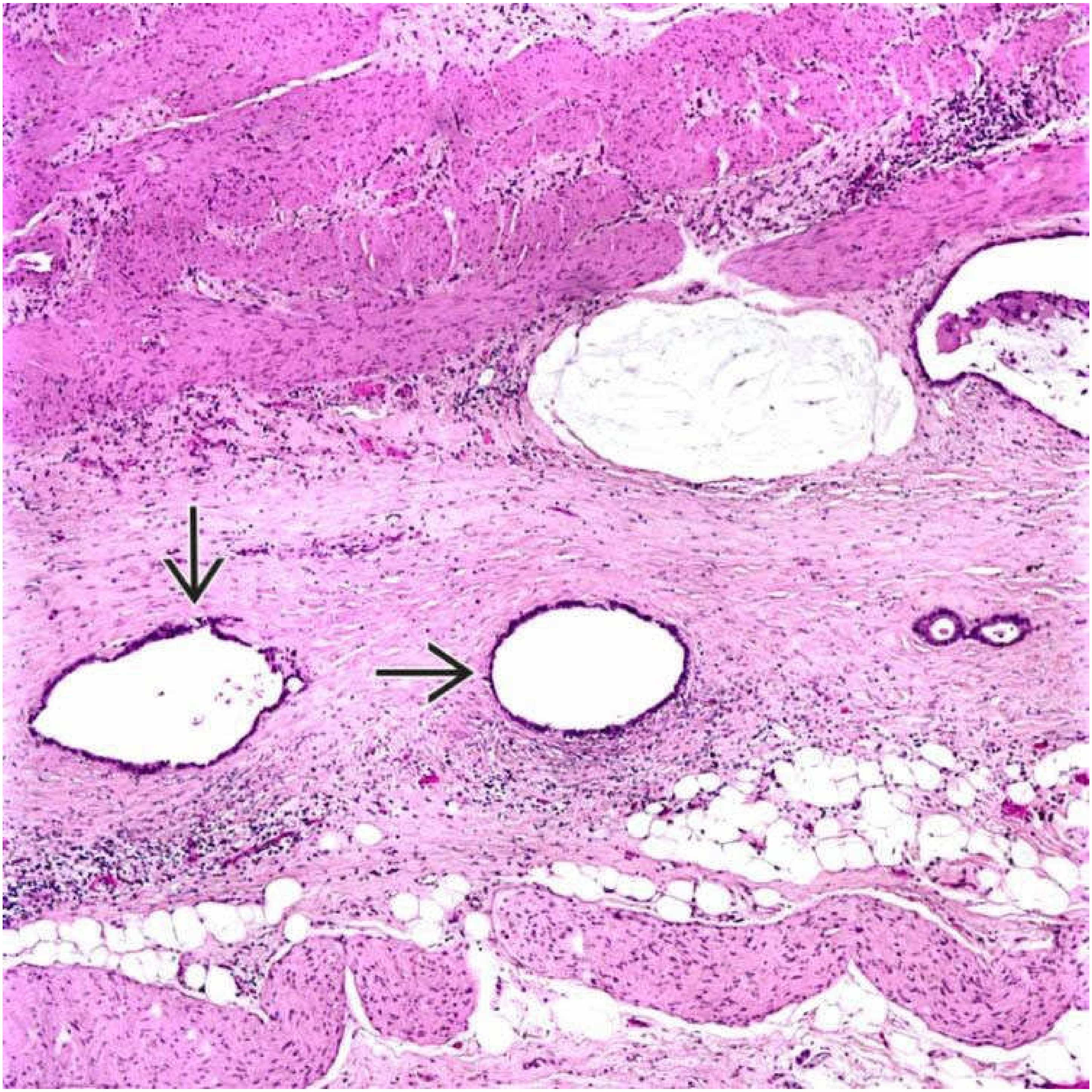
• Extremely rare; diagnosis based on clinical history &/or immunohistochemistry



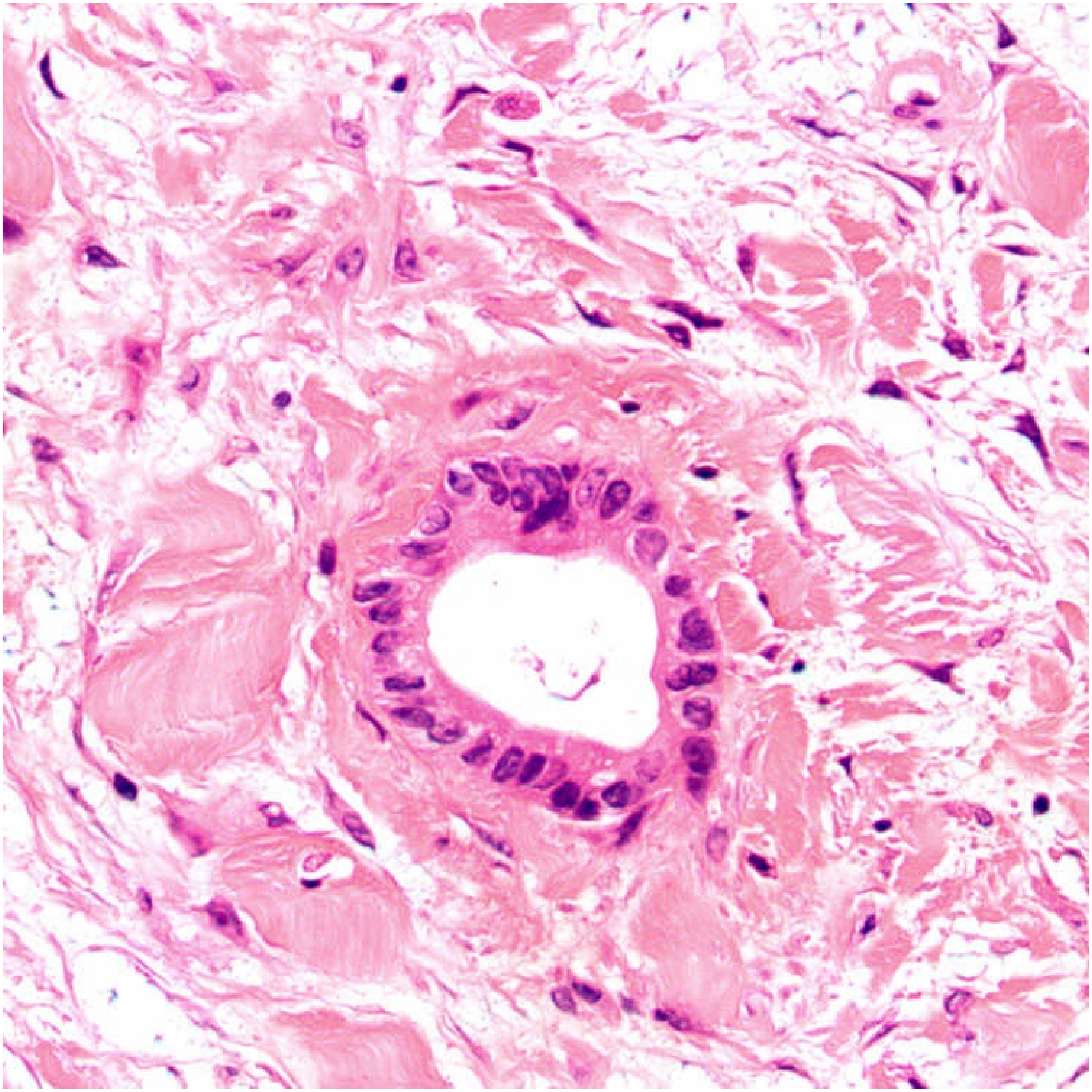
Gallbladder Adenocarcinoma and Benign Biliary Glands
These clearly malignant glands within desmoplastic stroma contrast nicely with the benign peribiliary glands ⇨ in the lower 1/2 of this image.



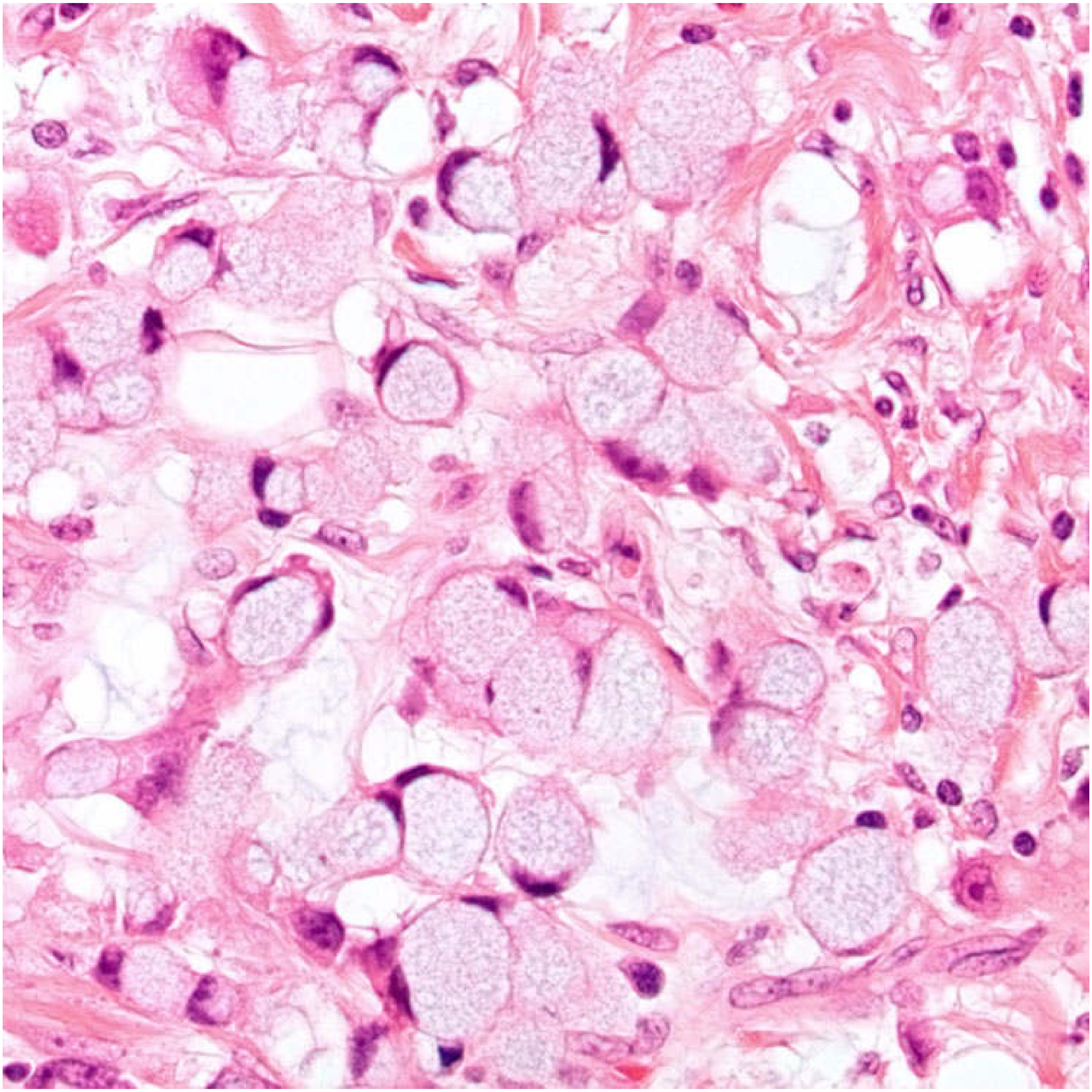
Gallbladder Adenocarcinoma, Well Differentiated
This section shows a few small, bland-appearing glands → infiltrating the perimuscular connective tissue in a case of well-differentiated gallbladder adenocarcinoma.



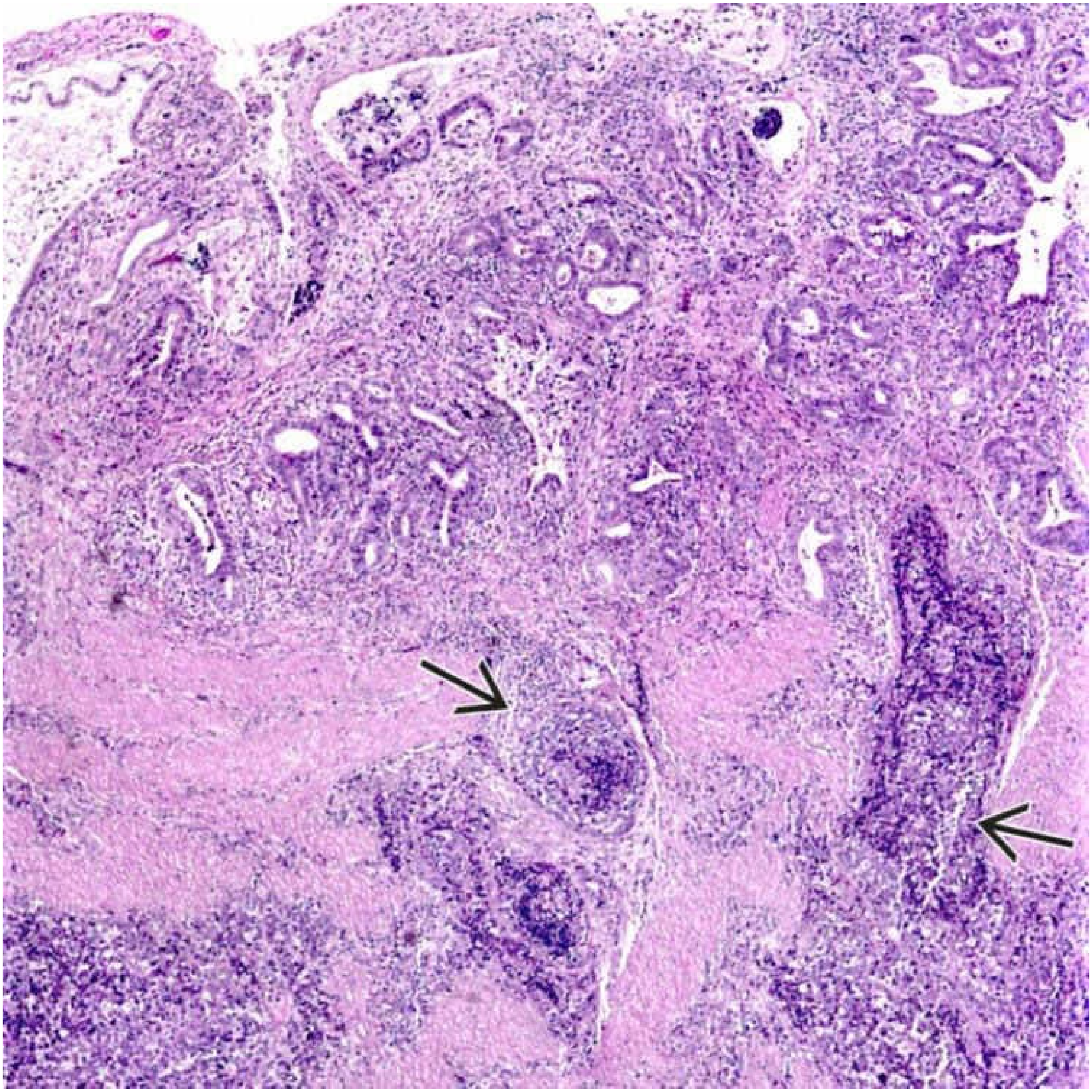
Gallbladder Adenocarcinoma, Well Differentiated
This very well-differentiated adenocarcinoma → has infiltrated through the muscular wall of the gallbladder to involve the perimuscular soft tissue. The alignment of the glands parallel to the muscular wall is a feature of neoplasia.



Gallbladder Adenocarcinoma, Well Differentiated
This relatively well-formed, yet malignant, gland infiltrates the wall in an example of well-differentiated gallbladder adenocarcinoma. Note the variation in nuclear size and the nuclear disarray.



Gallbladder Adenocarcinoma, Signet Ring Cell Type
This photomicrograph illustrates the signet ring cell pattern of gallbladder adenocarcinoma.



Gallbladder Adenocarcinoma, Neuroendocrine Carcinoma
This high-grade neuroendocrine carcinoma of the gallbladder features sheets of poorly differentiated neuroendocrine cells invading the gallbladder wall →. Note the overlying epithelial dysplasia.

SELECTED REFERENCES

1. Cariati, A, et al. Gallbladder cancers: associated conditions, histological types, prognosis, and prevention. *Eur J Gastroenterol Hepatol*. 2014; 26(5):562–569.
2. Dursun, N, et al. Mucinous carcinomas of the gallbladder: clinicopathologic analysis of 15 cases identified in 606 carcinomas. *Arch Pathol Lab Med*. 2012; 136(11):1347–1358.
3. Roa, JC, et al. Squamous cell and adenosquamous carcinomas of the gallbladder: clinicopathological analysis of 34 cases identified in 606 carcinomas. *Mod Pathol*. 2011; 24(8):1069–1078.

4. Singhi, AD, et al. Hyperplastic Luschka ducts: a mimic of adenocarcinoma in the gallbladder fossa. *Am J Surg Pathol*. 2011; 35(6):883–890.
5. Choi, SB, et al. Incidental gallbladder cancer diagnosed following laparoscopic cholecystectomy. *World J Surg*. 2009; 33(12):2657–2663.
6. Goldin, RD, et al. Gallbladder cancer: a morphological and molecular update. *Histopathology*. 2009; 55(2):218–229.
7. Henson, DE, et al. Carcinomas of the pancreas, gallbladder, extrahepatic bile ducts, and ampulla of vater share a field for carcinogenesis: a population-based study. *Arch Pathol Lab Med*. 2009; 133(1):67–71.
8. Furlan, A, et al. Gallbladder carcinoma update: multimodality imaging evaluation, staging, and treatment options. *AJR Am J Roentgenol*. 2008; 191(5):1440–1447.
9. Morine, Y, et al. Surgical strategy for advanced gallbladder carcinoma according to invasive depth of the tumor. *Hepatogastroenterology*. 2008; 55(88):1965–1970.

Adenocarcinoma of Extrahepatic Bile Ducts

KEY FACTS

Terminology

- Malignant biliary epithelial neoplasm arising from extrahepatic bile ducts (right and left hepatic ducts, common hepatic duct, and common bile duct)
  - 3 forms: Perihilar, distal, and diffuse
- Klatskin tumor: Perihilar tumor occurring at confluence of right and left hepatic ducts

Etiology/Pathogenesis

- Numerous risk factors, including developmental anomalies, flukes, primary sclerosing cholangitis

Clinical Issues

- Poor prognosis with 10% overall 5-year survival
  - Surgical resection is only hope for long-term survival
- Rare (incidence is 0.53-2.00 per 100,000)
- Primarily 6th and 7th decades of life
- Nonspecific symptoms, signs of biliary obstruction
- Elevated serum CA19-9, CEA-M, CA125

Microscopic

- Wide spectrum of histologic appearances
    - Malignant glands are arranged in haphazard pattern, infiltrating duct wall
    - Often associated with desmoplastic stroma
    - Nuclear pleomorphism with increased N:C ratio, nuclear grooves, and brisk mitotic activity
  - Cytologic features may be deceptively bland
- Frequent lymphovascular &/or perineural invasion

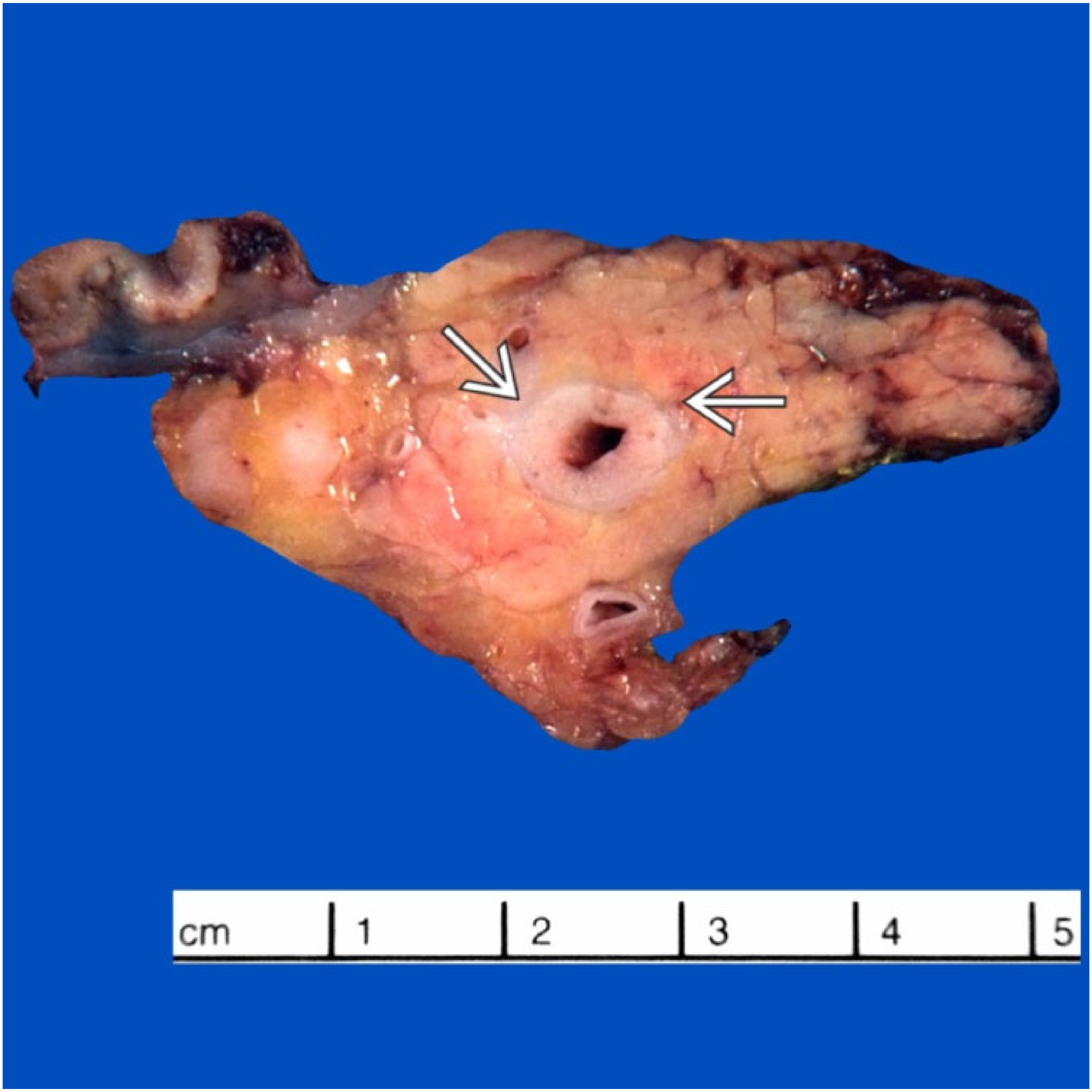
Ancillary Tests

- Positive: CK-PAN, CK7, CK19, CEA-M, CA19-9, MUC1, and MUC5AC

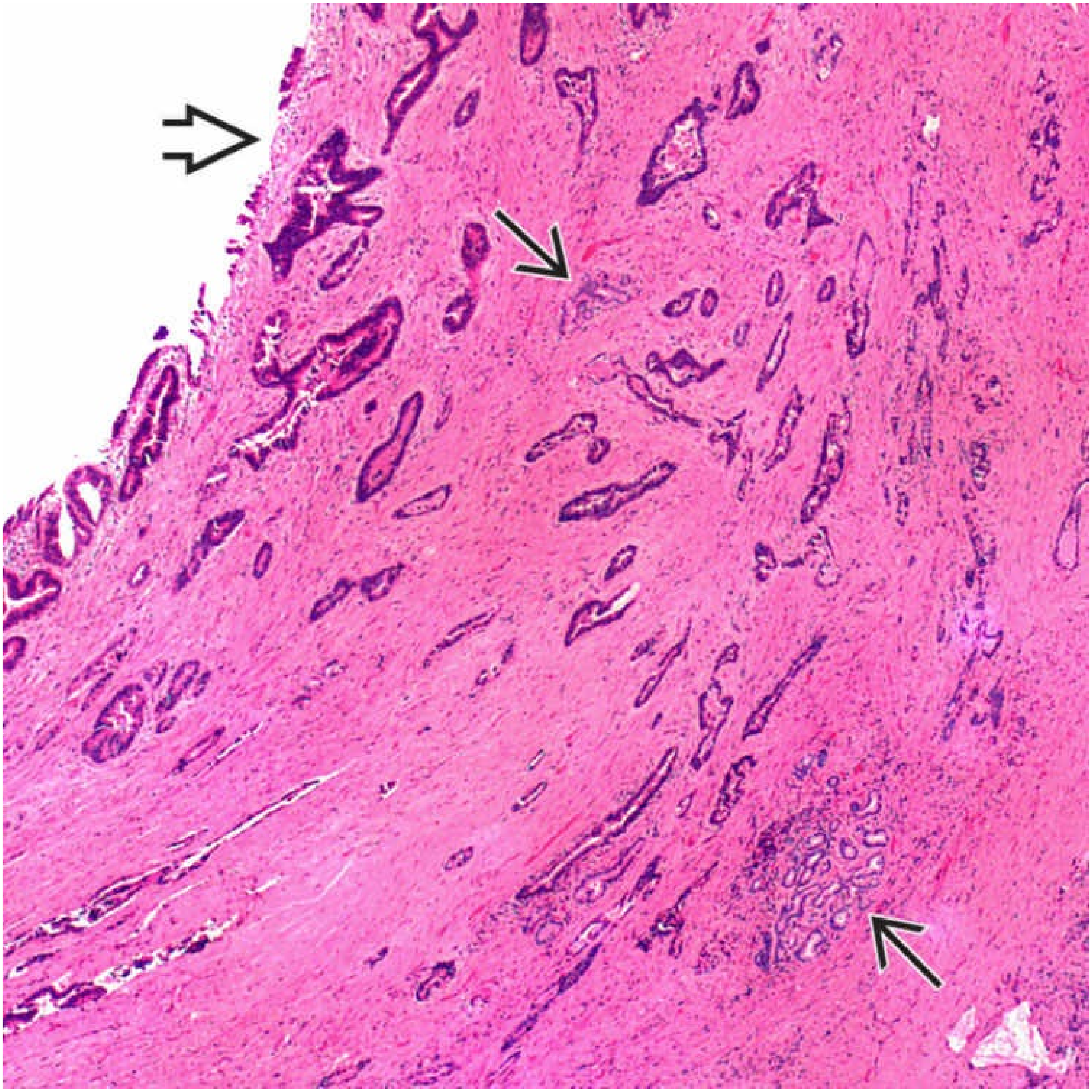
- CK20, CDX-2 positive in < 50% of cases

Top Differential Diagnoses

- Reactive periductal glands
- Pancreatic ductal carcinoma: Indistinguishable histologically and immunophenotypically

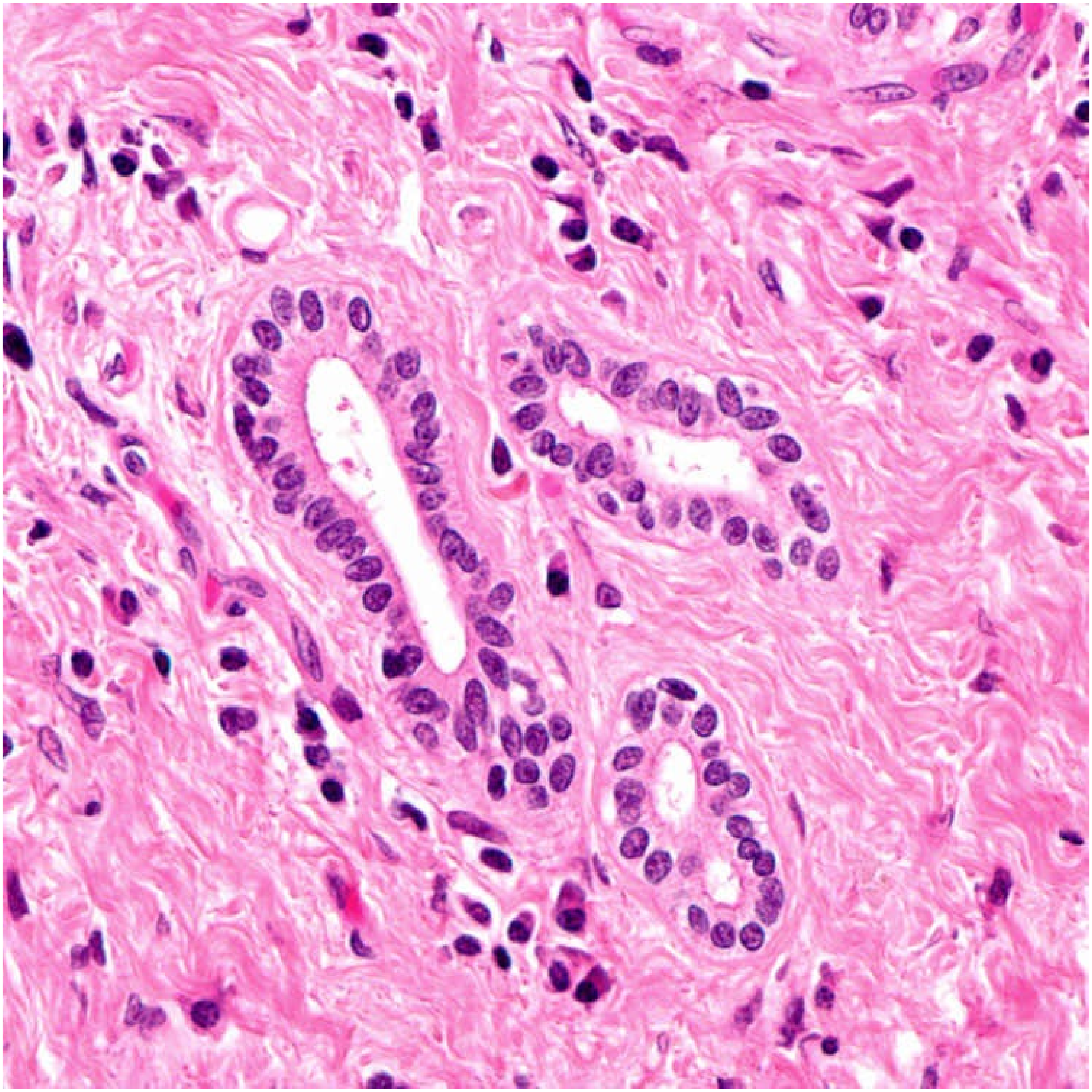


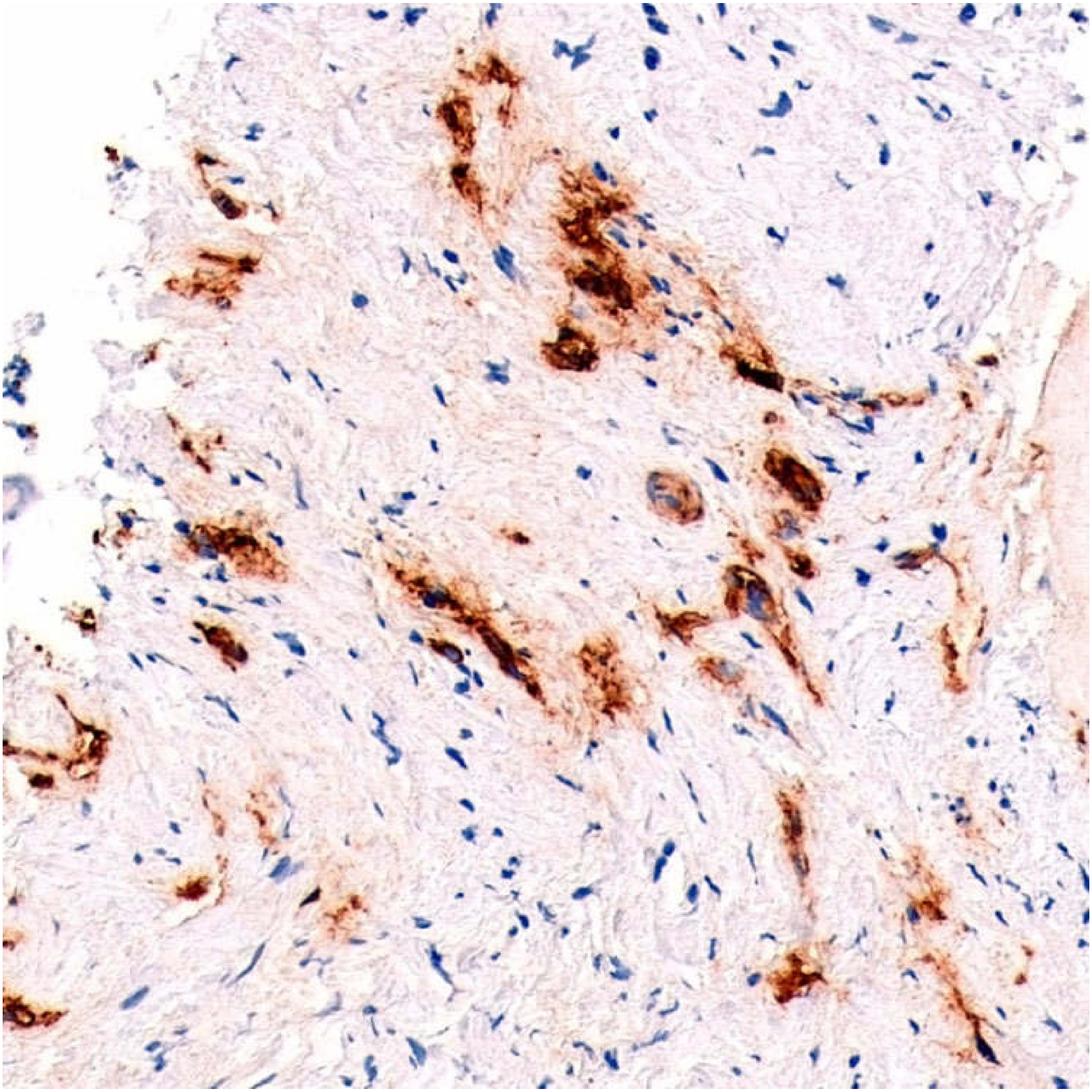
Gross Appearance
This cross section from a Whipple resection shows distal bile duct carcinoma involving the intrapancreatic portion of the common bile duct. Note the marked thickening of the duct wall ⇒ .



Widely Spaced Irregular Glands

This case of extrahepatic cholangiocarcinoma features widely spaced, irregular glands infiltrating the duct wall. The duct lumen is partially denuded ⇨. Note the presence of residual benign periductal glands arranged in a lobular pattern → .


High-Power View
These tumors are often very well differentiated, such as this case featuring well-formed glandular structures lined by a single layer of cuboidal epithelial cells with minimal cytologic atypia.



CK7
An extrahepatic bile duct biopsy shows poorly differentiated adenocarcinoma with cord-like clusters and individual cells infiltrating desmoplastic stroma. The tumor cells are immunoreactive with CK7.

TERMINOLOGY

Synonyms

- Extrahepatic cholangiocarcinoma

Definitions

- Malignant biliary epithelial neoplasm arising from right or left hepatic duct, common hepatic duct, or

common bile duct

- Perihilar: Arises in extrahepatic bile ducts upstream from origin of cystic duct (70-80%)
  - Klatskin tumor: Perihilar tumor occurring at confluence of right and left hepatic ducts
- Distal: Arises in common bile duct, including intrapancreatic portion, above ampulla of Vater (20-30%)
- Diffuse (~ 2%)

ETIOLOGY/PATHOGENESIS

Risk Factors

- Developmental (choledochal cyst, abnormal choledochopancreatic junction)
- Primary sclerosing cholangitis
- Parasitic infection (i.e., flukes)
- Familial adenomatous polyposis
- Molecular alterations [*KRAS* mutations (30%), overexpression of p53 oncoprotein (50%)]

CLINICAL ISSUES

Epidemiology

- Incidence
  - 0.53-2.00 per 100,000 in population
- Age
  - Primarily 6th and 7th decades of life
- Sex
  - Slight male predominance

Presentation

- Nonspecific symptoms: Abdominal pain, malaise, anorexia, nausea/vomiting, weight loss
- Signs of biliary obstruction: Jaundice, pruritus, acholic stools, dark urine

Laboratory Tests

- Elevated serum CA19-9, CEA-M, CA125

Treatment

- Surgery plus chemoradiation

Prognosis

- Poor; overall 10% 5-year survival

IMAGING

Ultrasonographic Findings

- Duct dilation indicative of downstream obstruction

CT and MR Findings

- Infiltrative pattern (duct wall thickening, obliteration of duct lumen) or mass lesion

ERCP Findings

- Bile duct stricture

MACROSCOPIC

General Features

- Polypoid, nodular, constricting/stenotic, or diffusely infiltrating
- Firm, white, gritty, cut surface

MICROSCOPIC

Histologic Features

- Very variable morphologic appearance with numerous histologic variants
  - Glands may be well formed, irregular, abortive, cribriforming, or form papillary structures
    - Randomly and haphazardly infiltrate duct wall; often widely spaced
    - Individual infiltrating cells may be present as well
  - Cytologic features
    - Deceptively bland to overtly high-grade nuclei
      - Raisinoid nuclei with nuclear grooves
      - Nuclear anisocytosis
    - Acidophilic, basophilic, granular, pale, clear, foamy, or microvesicular cytoplasm
- Prominent desmoplastic stroma
- Varying amounts of intraluminal or extracellular mucin and tumor necrosis
- Frequent lymphovascular &/or perineural invasion
- Frequent association with epithelial dysplasia or carcinoma in situ

ANCILLARY TESTS

Immunohistochemistry

- Positive: CK-PAN, CK7, CK19, CEA-M, CA19-9, MUC1, and MUC5AC

- CK20, CDX-2 positive in < 50% of cases

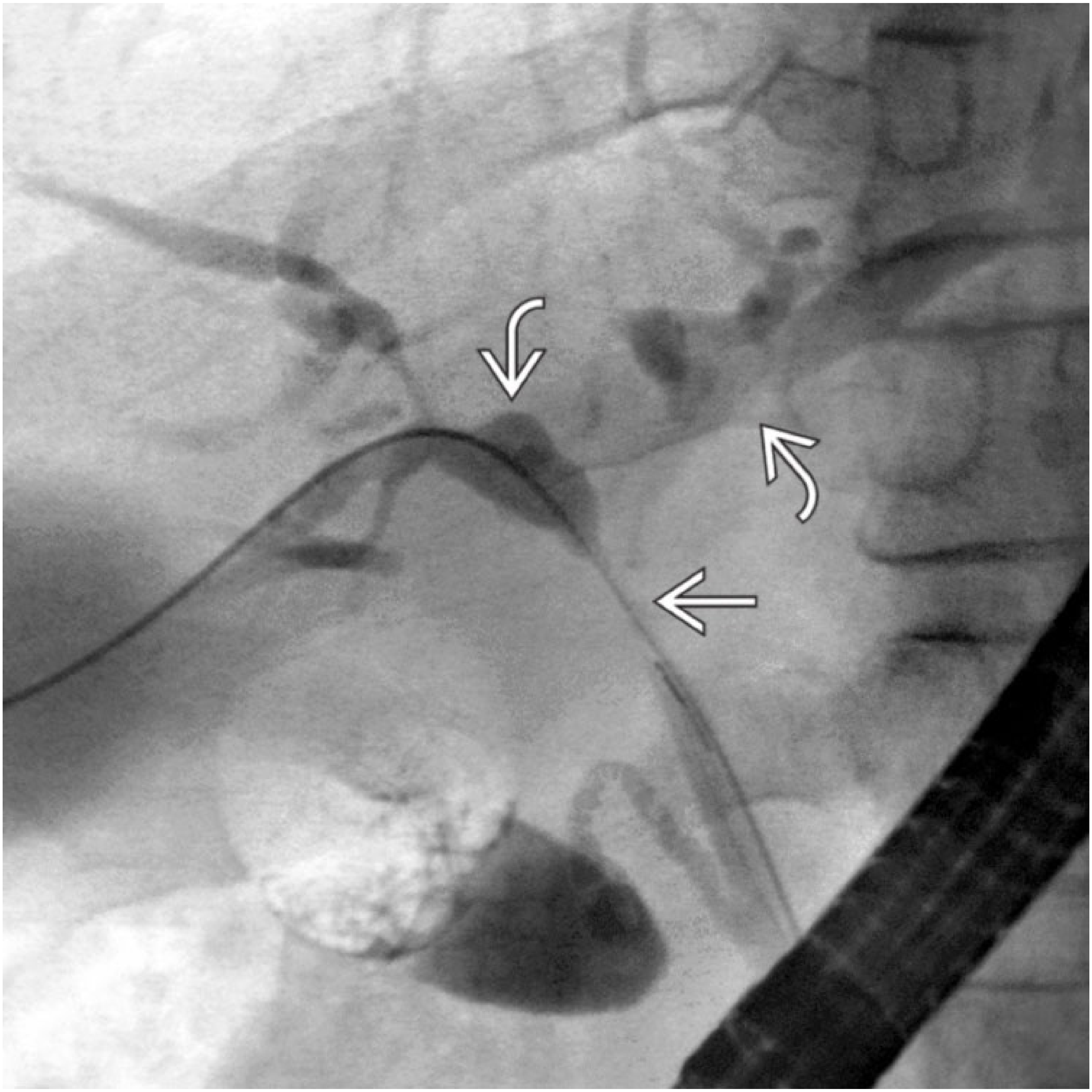
DIFFERENTIAL DIAGNOSIS

Reactive Periductal Glands

• Preserved lobular architecture with uniform, noninfiltrating glands; often history of stent

Secondary Involvement by Pancreatic Ductal Adenocarcinoma

• Indistinguishable histologically and immunophenotypically; clinical history, image findings helpful

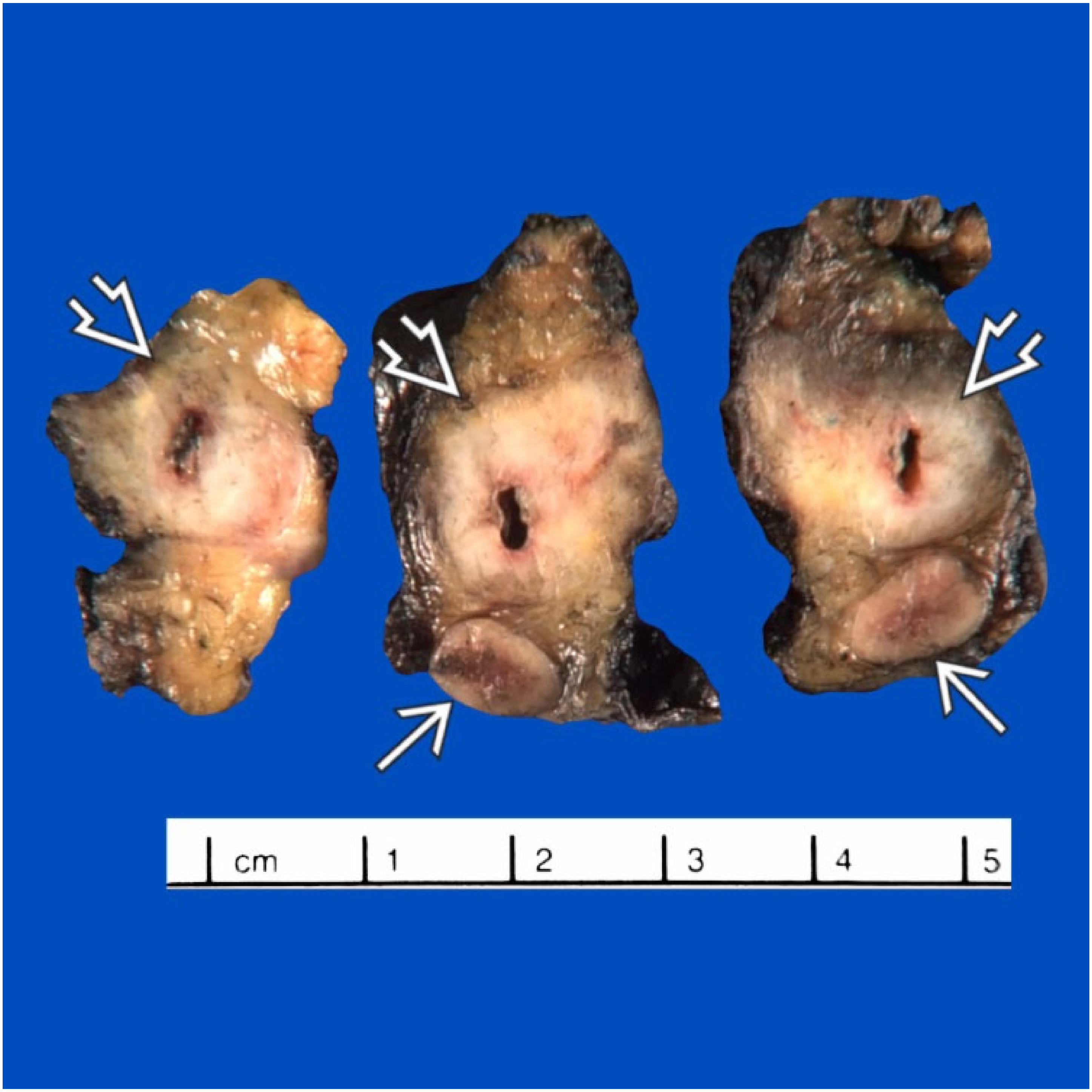


ERCP

ERCP shows obstruction at the confluence of the right and left hepatic ducts, with upstream bile duct dilation, consistent with a Klatskin tumor.

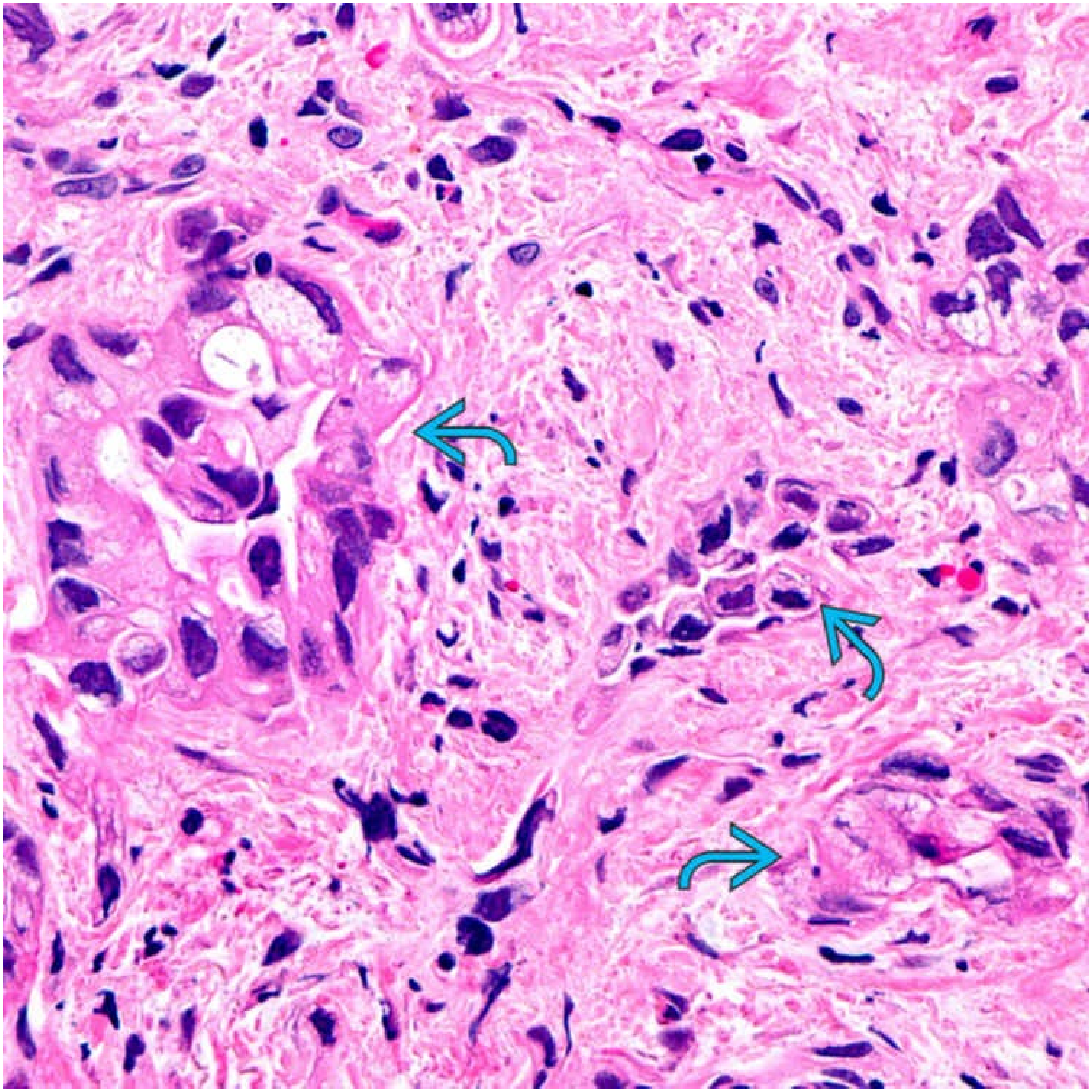
CT

Coronal contrast-enhanced CT shows segmental wall thickening and hyperenhancement of the common bile duct →. An ill-defined outer duct wall is suggestive of invasion beyond the duct. Note dilated upstream intrahepatic bile ducts ↷ .



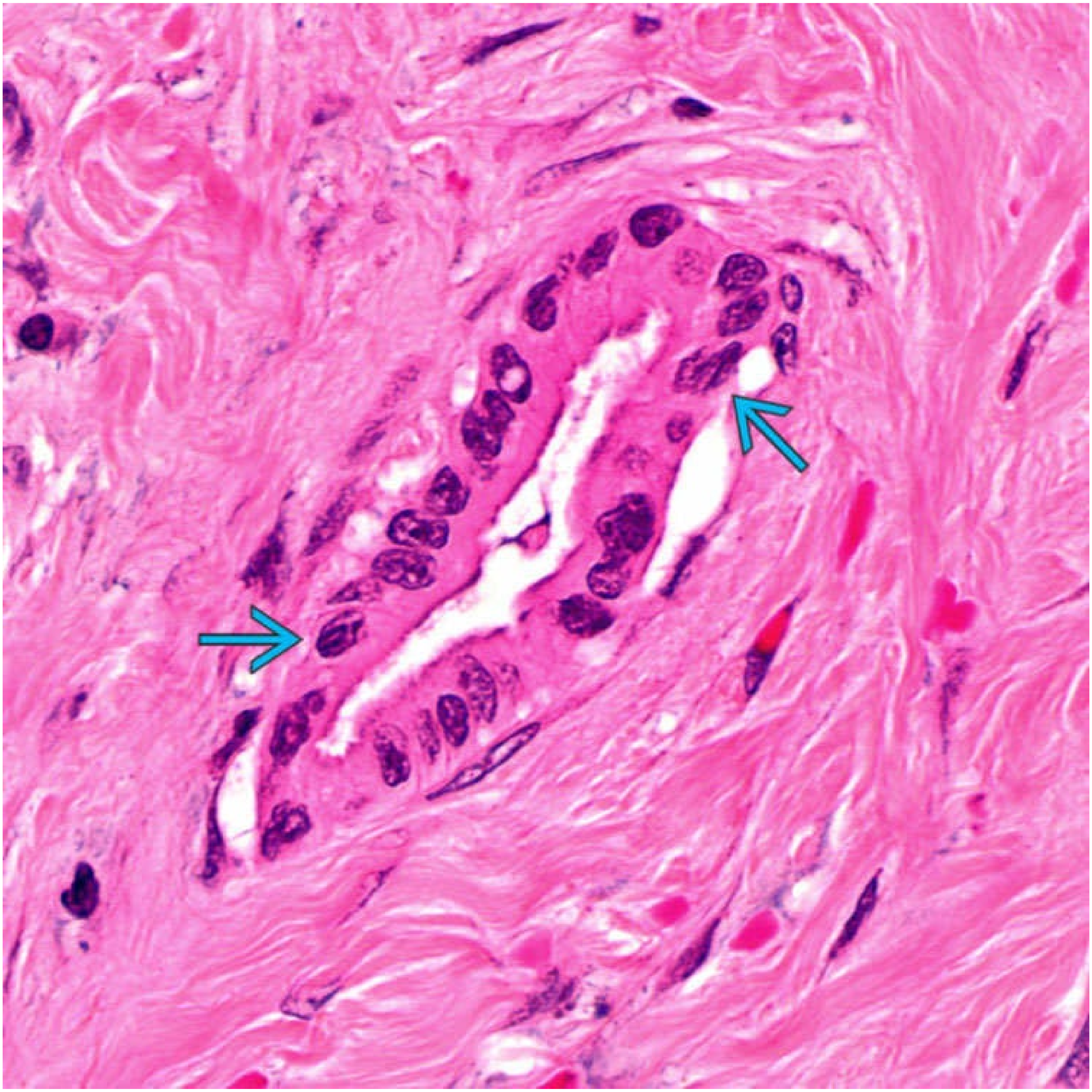
Gross Appearance

A segmental resection for perihilar bile duct carcinoma shows marked thickening of the common hepatic duct with firm, white cut surfaces ⇨ representing infiltrating tumor. A portion of markedly dilated cystic duct ⇨ is present as well.



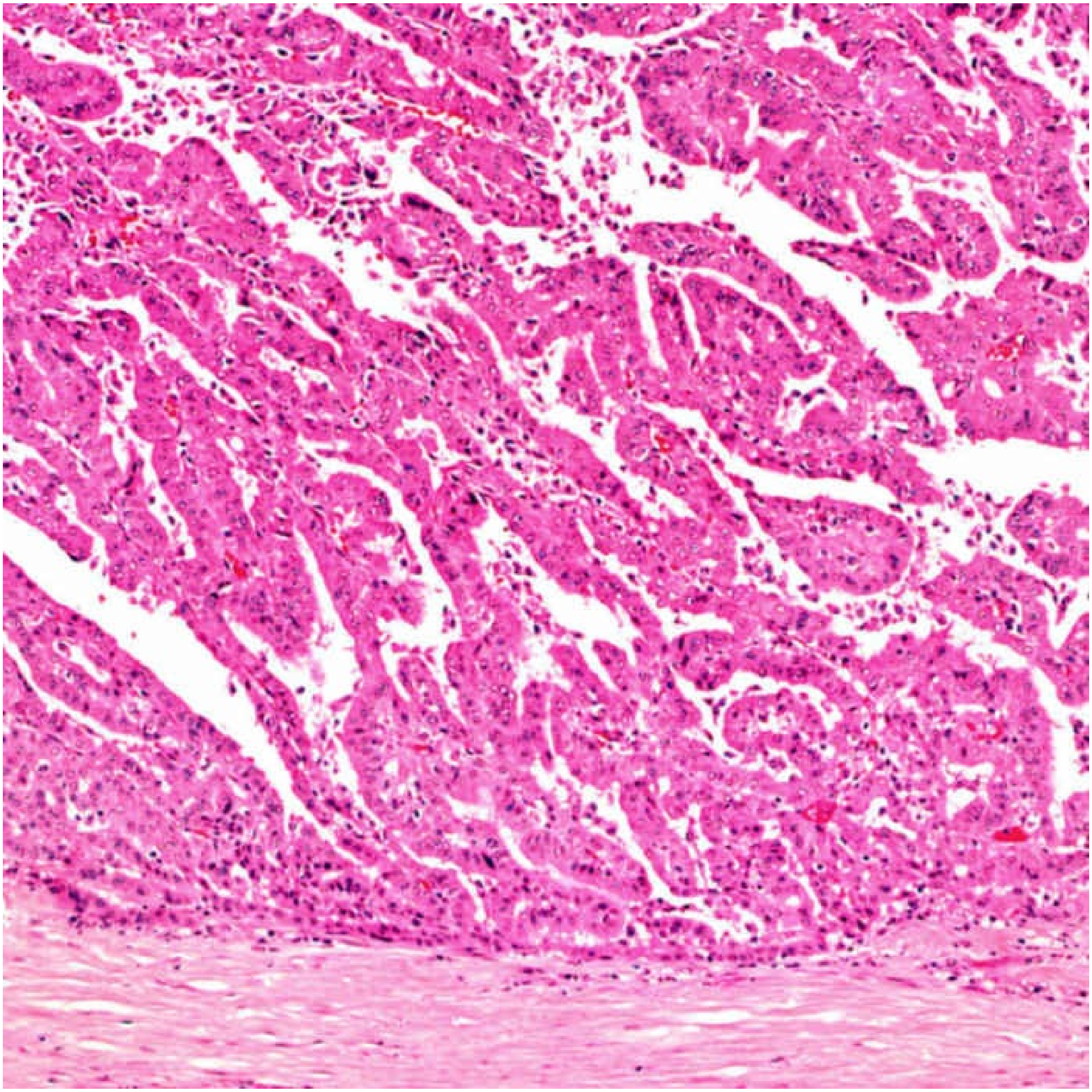
Stroma

This bile duct biopsy contains a moderately differentiated adenocarcinoma characterized by scattered glands infiltrating dense fibrotic stroma, typical of cholangiocarcinoma. The neoplastic glands are lined by pleomorphic tumor cells with foamy cytoplasm.



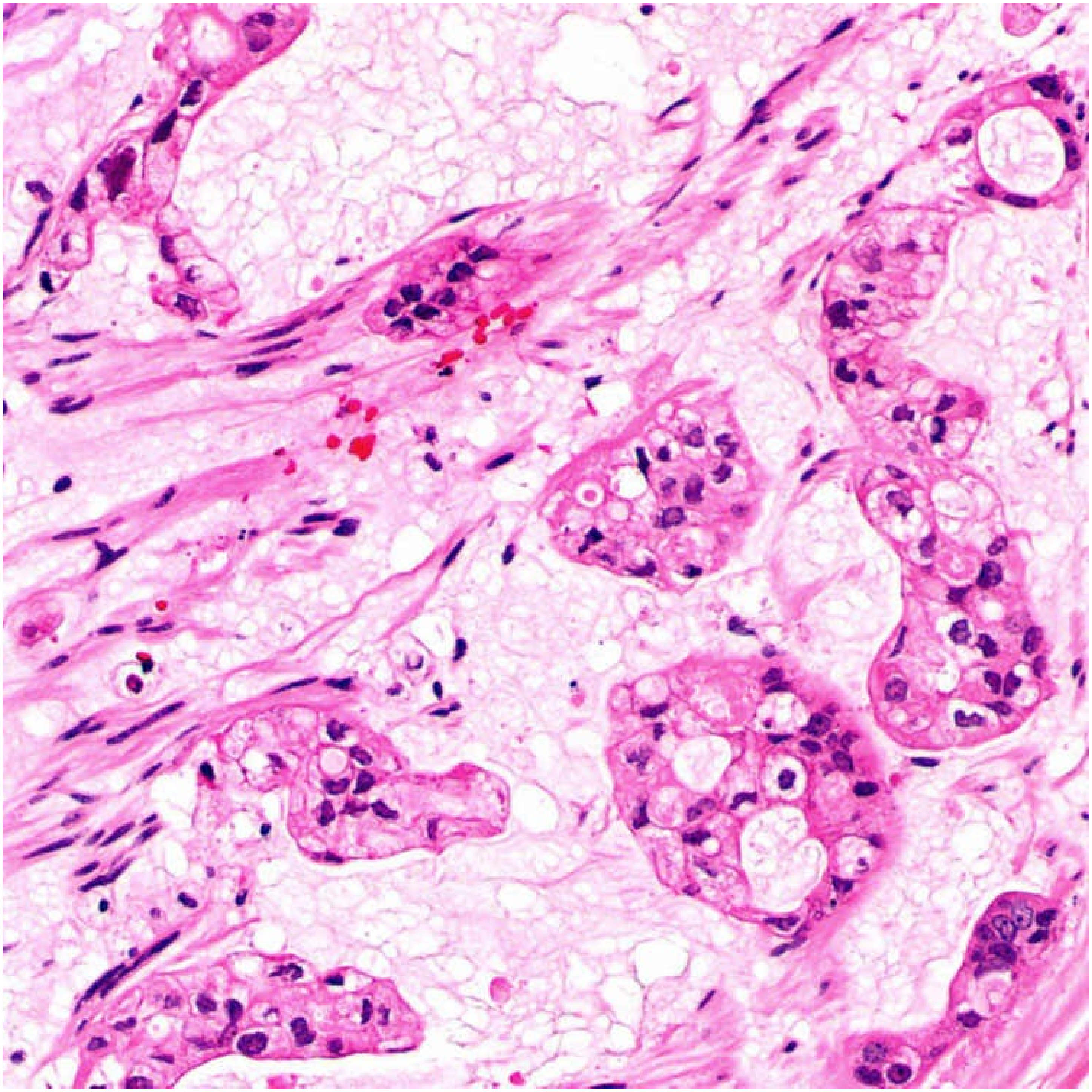
Cytologic Features

Adenocarcinomas of the extrahepatic bile duct may be very well differentiated. This well-formed gland is lined by raisinoid tumor cells with nuclear grooves →, irregular nuclear membranes, and variation in nuclear size and shape.

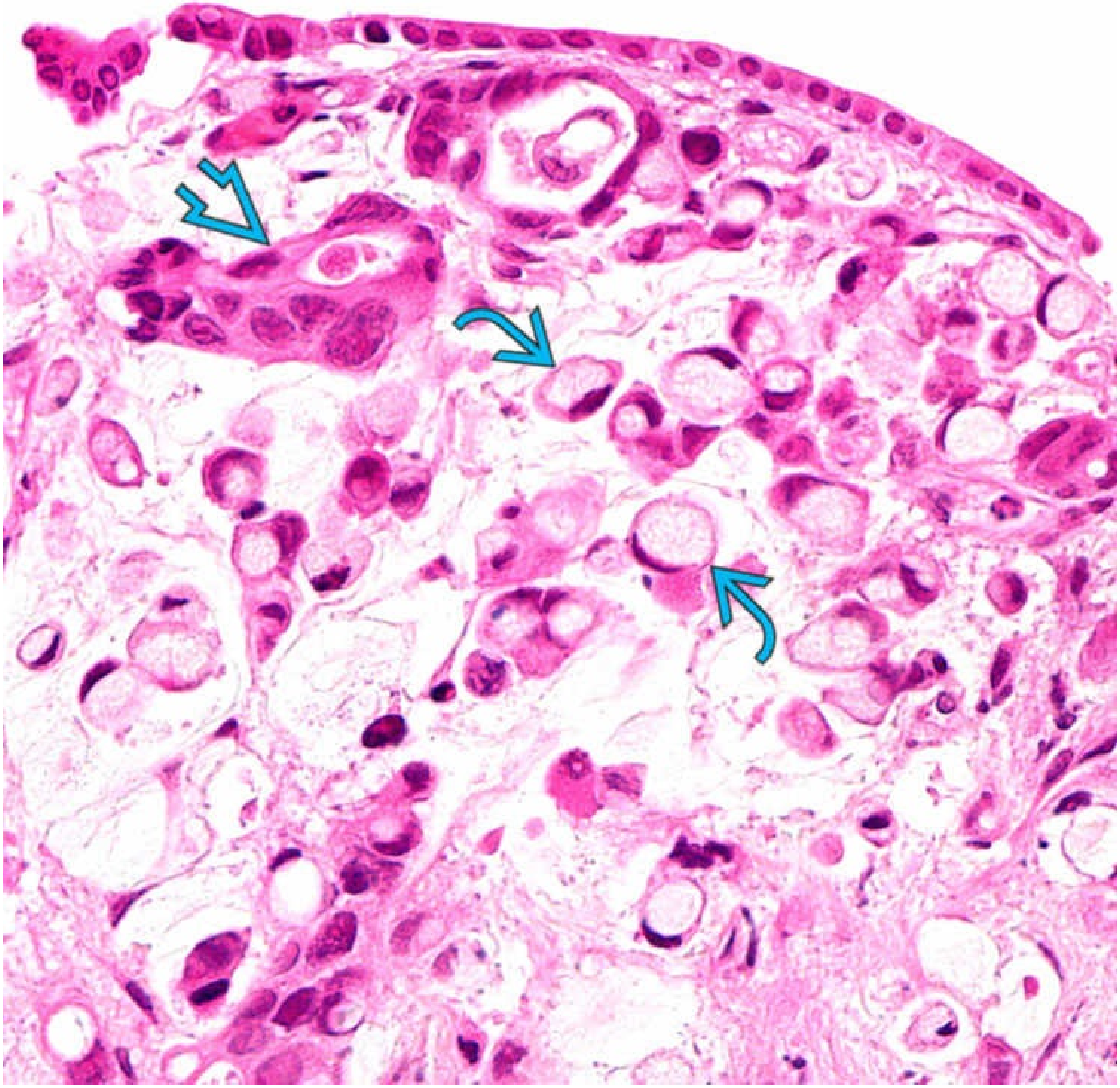


Papillary Type

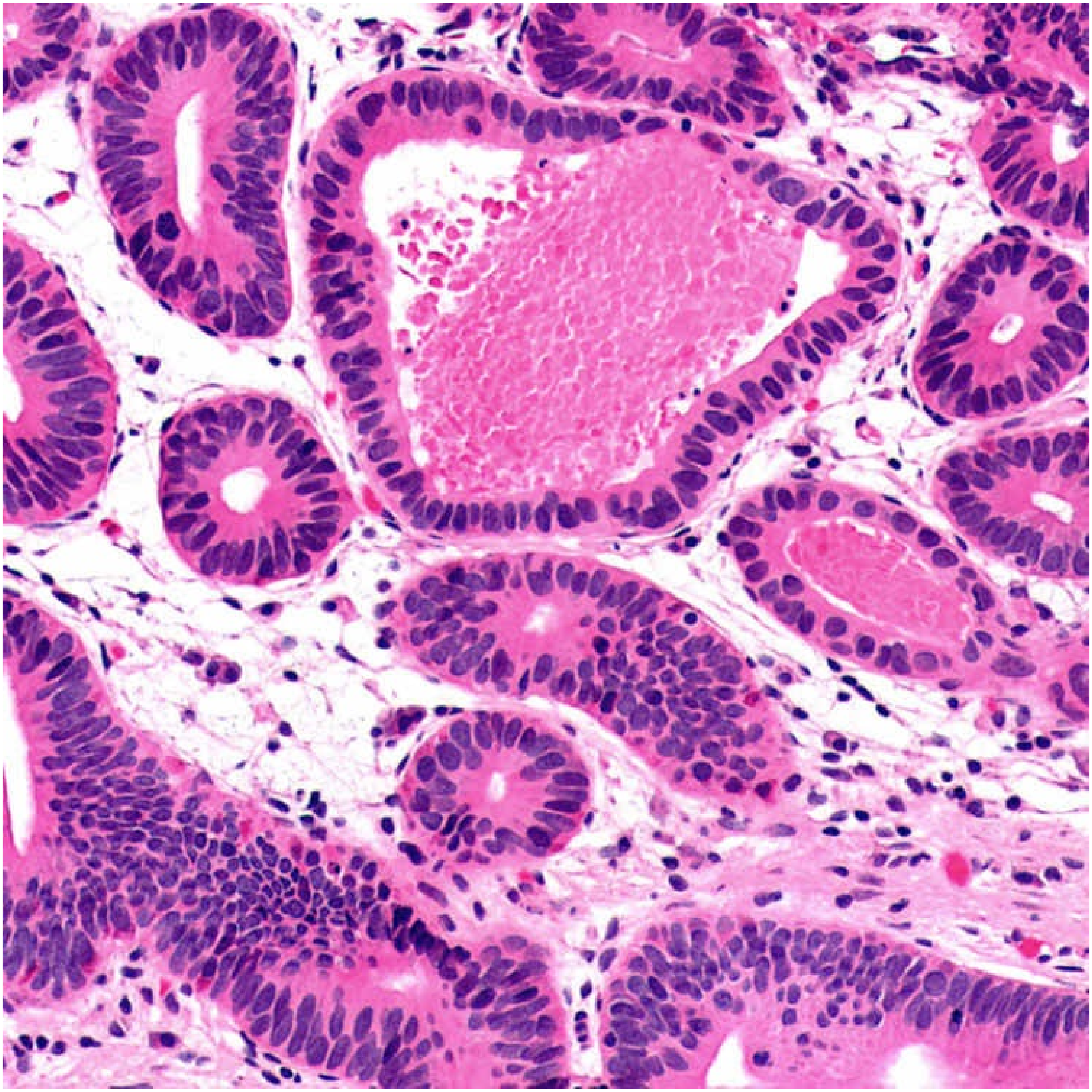
The papillary variant consists of a proliferation of complex papillary structures within the lumen of the duct, lined by cuboidal or columnar epithelial cells. These tumors can be invasive or noninvasive, as seen here.

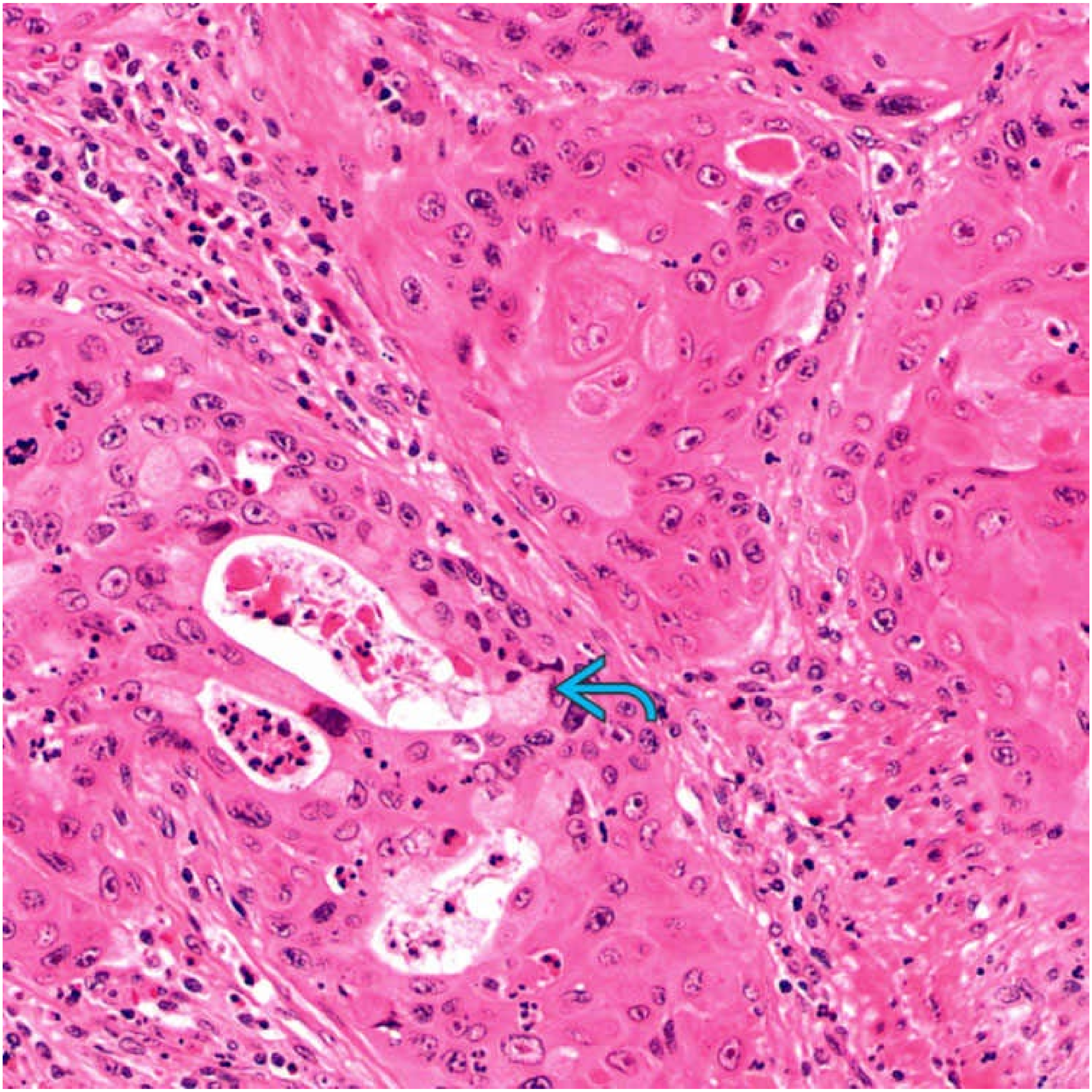


Mucinous Type
In the mucinous variant, extracellular mucin should comprise > 50% of tumor volume. Malignant glands are distended with mucin, and clusters of tumor cells float in mucin lakes.

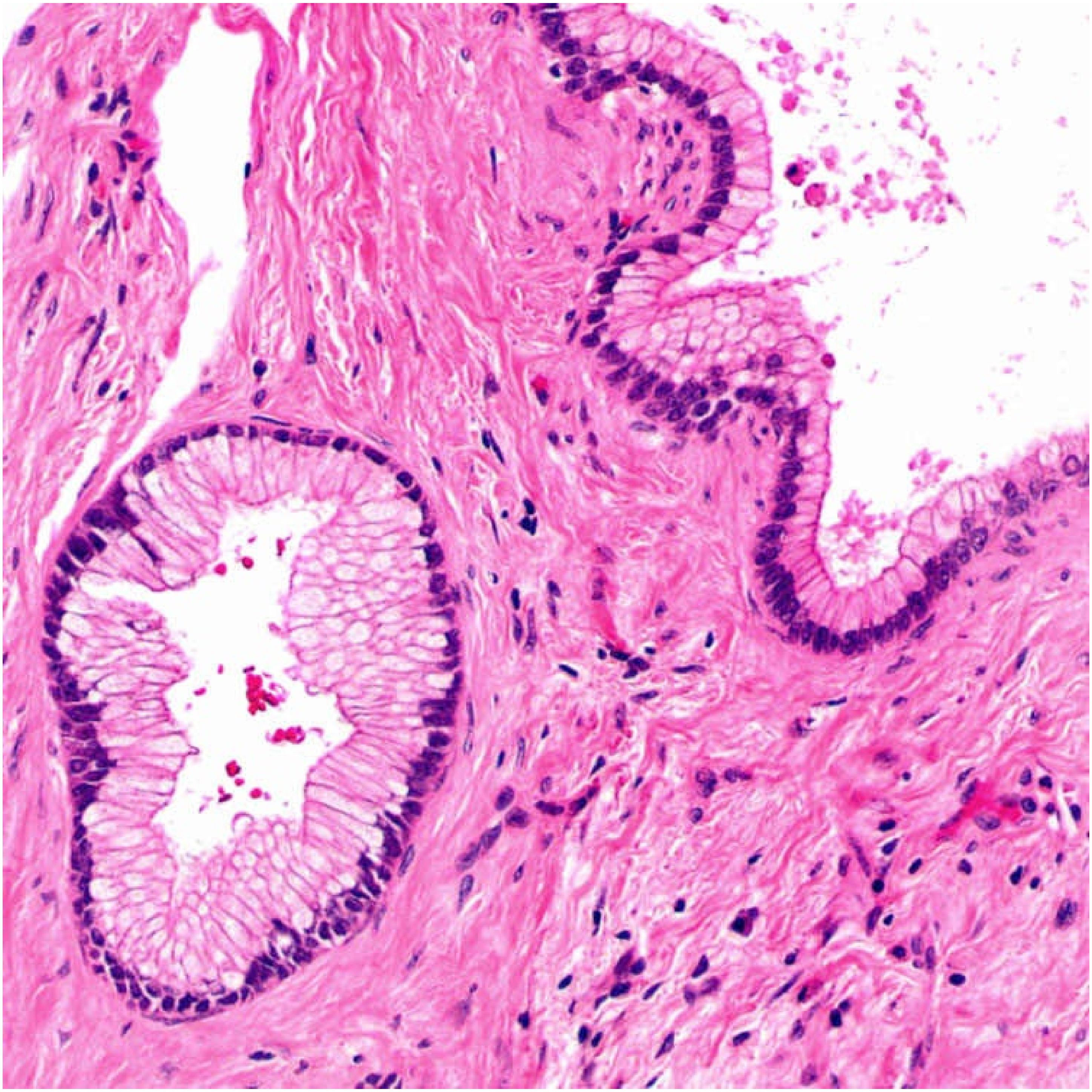


Signet Ring Cell Type
A bile duct biopsy shows numerous diffusely infiltrating signet ring cells invading the duct wall. Poorly formed glandular structures are rarely seen. The overlying biliary epithelium appears cytologically unremarkable. In this variant, signet ring cells should constitute > 50% of the tumor.


Intestinal Type
Intestinal-type adenocarcinoma of the extrahepatic bile duct closely resembles adenocarcinoma of the colon. Note the presence of necrotic debris within the lumina of neoplastic glands.

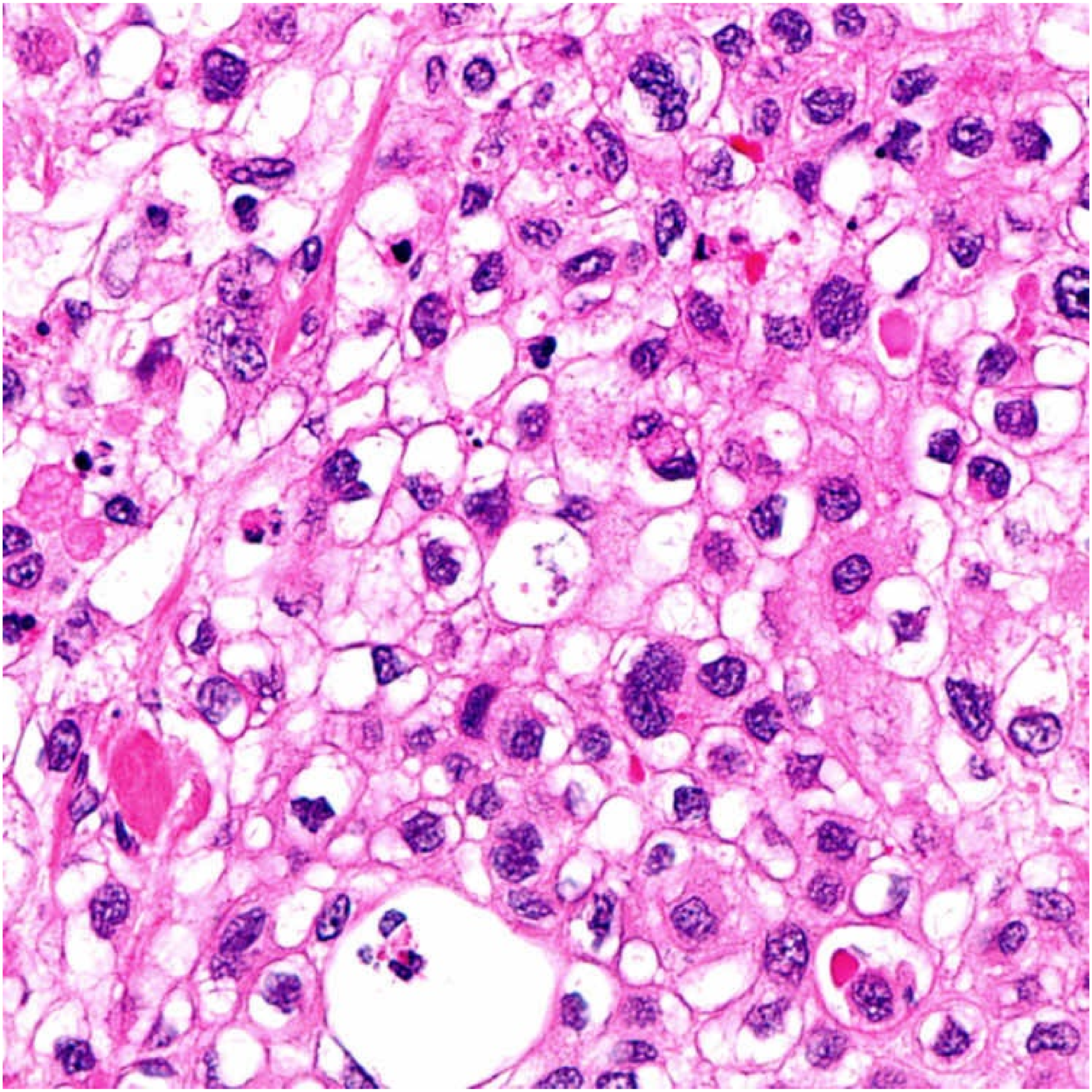


Adenosquamous Type
In the adenosquamous variant, the tumor is composed of both glandular and squamous elements. A predominantly glandular tumor should be at least 25% squamous to be classified as such, but a squamous tumor with any gland formation can be called adenosquamous. Note the mucin in the glands .



Gastric Foveolar Type

This tumor shows well-formed glands lined by a single layer of tall, columnar, mucin-secreting cells with basal nuclei and microvesicular cytoplasm, resembling gastric foveolar epithelium. Note the striking lack of cytologic atypia.



Clear Cell Type
Poorly differentiated adenocarcinoma of the extrahepatic bile duct with clear cell features shows sheets of cells with irregular nuclei, clear cytoplasm, and distinct cell borders, resembling clear cell carcinoma of the kidney.

SELECTED REFERENCES

1. Bergquist, A, et al. Epidemiology of cholangiocarcinoma. *Best Pract Res Clin Gastroenterol*. 2015; 29(2):221–232.
2. Pomianowska, E, et al. Reclassification of tumour origin in resected periampullary adenocarcinomas reveals underestimation of distal bile duct cancer. *Eur J Surg Oncol*. 2012; 38(11):1043–1050.
3. Patel, T. Cholangiocarcinoma. *Nat Clin Pract Gastroenterol Hepatol*. 2006; 3(1):33–42.

4. Welzel, TM, et al. Impact of classification of hilar cholangiocarcinomas (Klatskin tumors) on the incidence of intra- and extrahepatic cholangiocarcinoma in the United States. *J Natl Cancer Inst*. 2006; 98(12):873–875.
5. Shaib, Y, et al. The epidemiology of cholangiocarcinoma. *Semin Liver Dis*. 2004; 24(2):115–125.
6. Jarnagin, WR. Cholangiocarcinoma of the extrahepatic bile ducts. *Semin Surg Oncol*. 2000; 19(2):156–176.

Squamous/Adenosquamous Carcinoma, Gallbladder

KEY FACTS

Terminology

- Malignant epithelial neoplasms of gallbladder composed of either pure squamous component or both squamous and glandular components

Etiology/Pathogenesis

- Neoplastic transformation from squamous metaplasia of gallbladder mucosa
  - Metaplasia → dysplasia → carcinoma sequence
- Progression from preexisting adenocarcinoma
  - Considered “metaplastic carcinoma” like that in breast
- Gallstones present in 40-68% of cases

Clinical Issues

- 1-12% of all gallbladder carcinomas
  - Pure squamous cell carcinoma: 0.5-3.0%
- Worse prognosis than conventional gallbladder adenocarcinoma stage by stage

Macroscopic

- White-tan, firm or friable, intraluminal fungating mass
- Diffuse thickening and induration of gallbladder wall
- May involve adjacent organs, including liver, colon, stomach, duodenum, omentum, pancreas, extrahepatic bile ducts, hepatic arteries

Microscopic

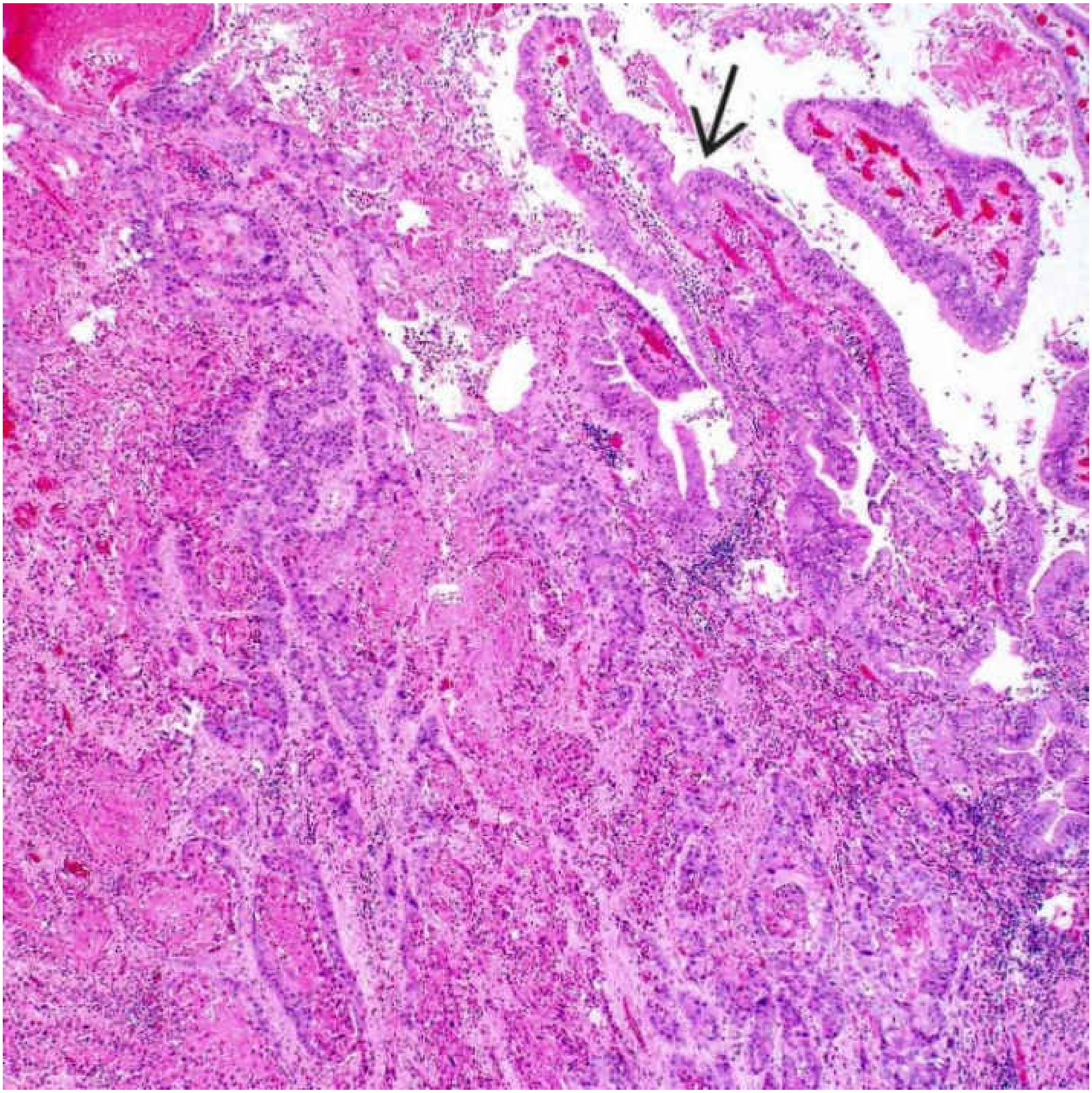
- Squamous cell carcinoma
  - Composed entirely of squamous component

- Spindle cells may predominate in poorly differentiated/sarcomatoid cases

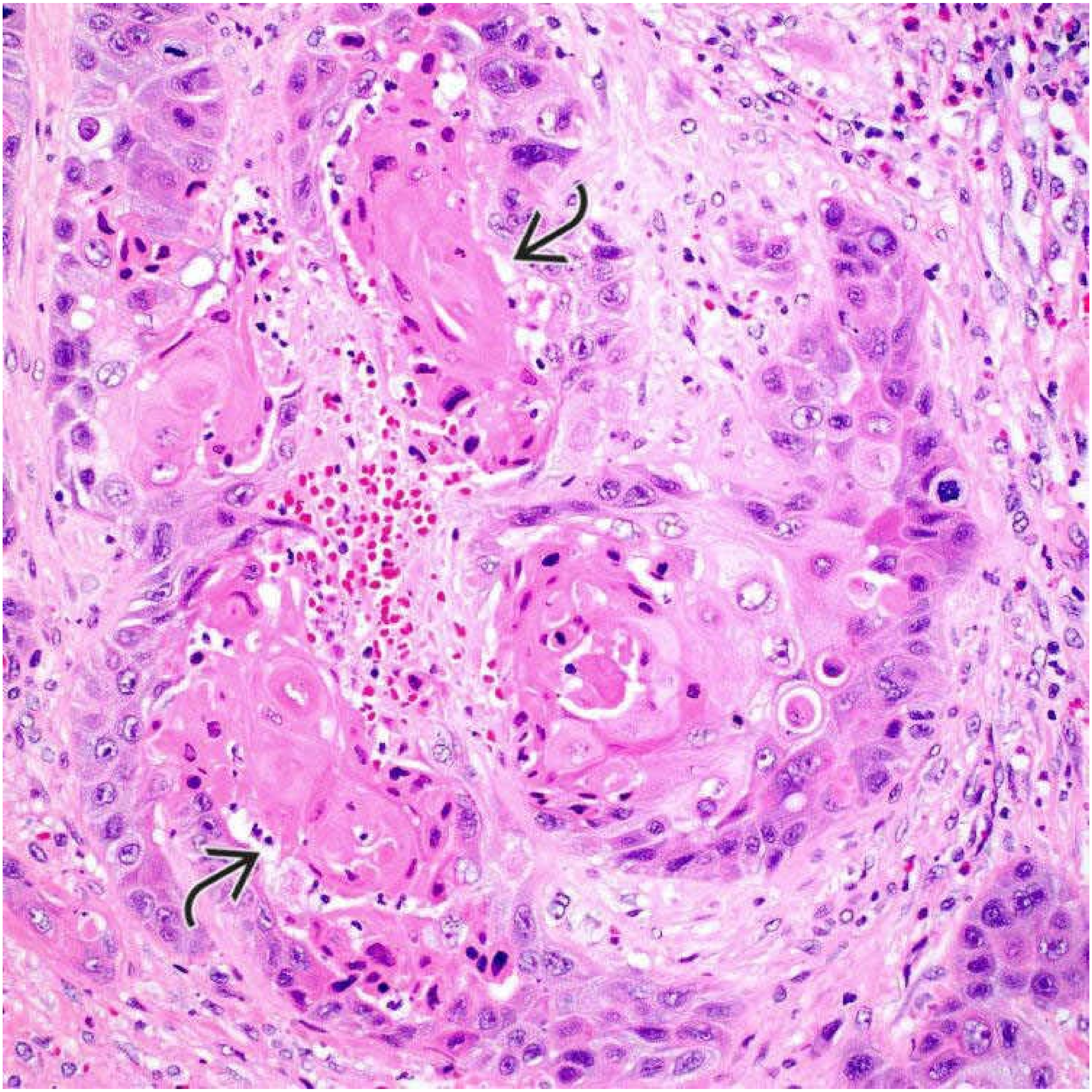
- Adenosquamous carcinoma has both malignant glandular and squamous components
  - Glandular component: Any amount
  - Squamous component: ≥ 25% of tumor volume

Top Differential Diagnoses

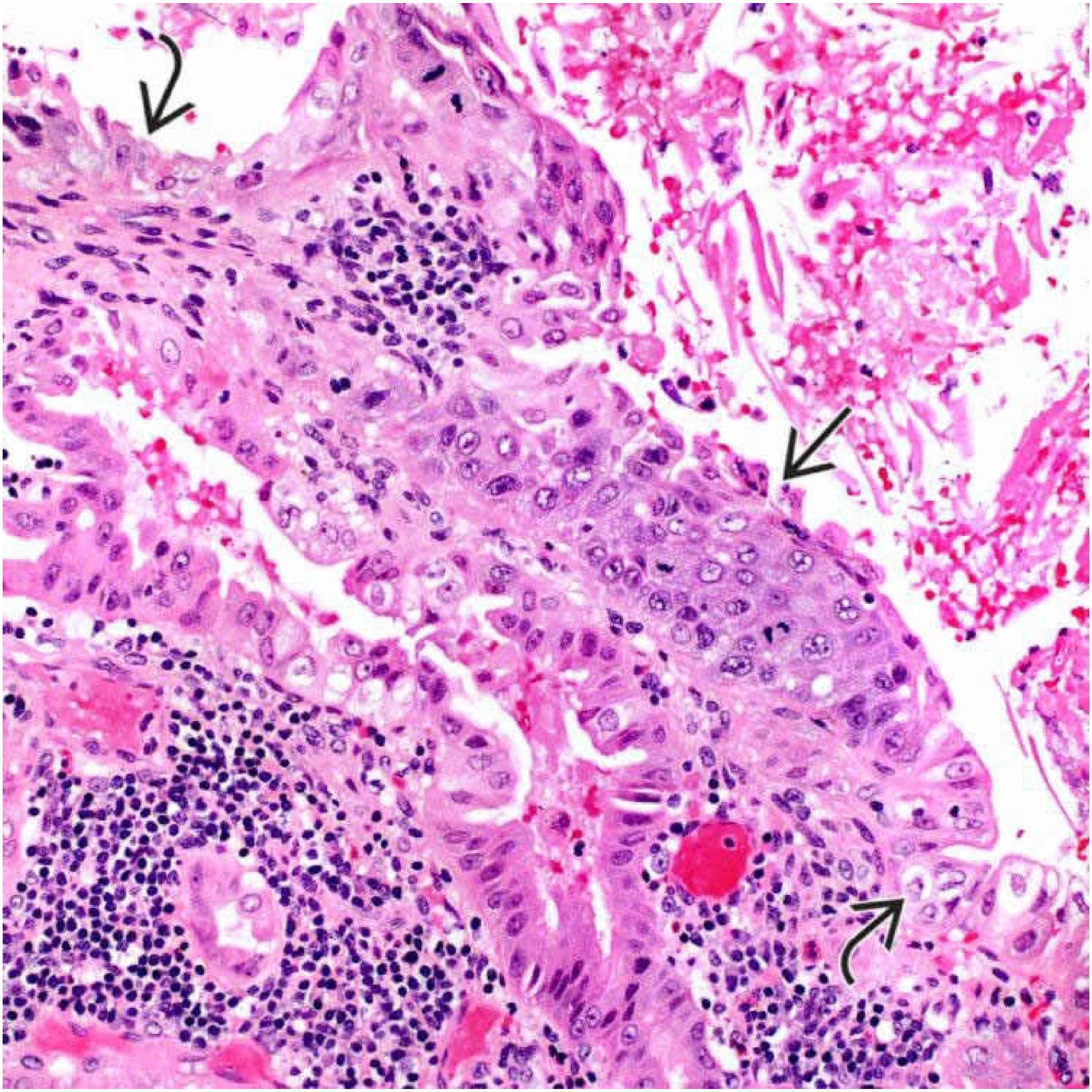
- Metastatic squamous cell carcinoma



Squamous Cell Carcinoma
This primary squamous cell carcinoma was resected from a 84-year-old man who presented with acute cholecystitis. A 4.6-cm intraluminal mass was found in the fundus in cholecystectomy specimen. Extensive sampling did not reveal glandular component. Note the presence of partially preserved gallbladder mucosa → over tumor.

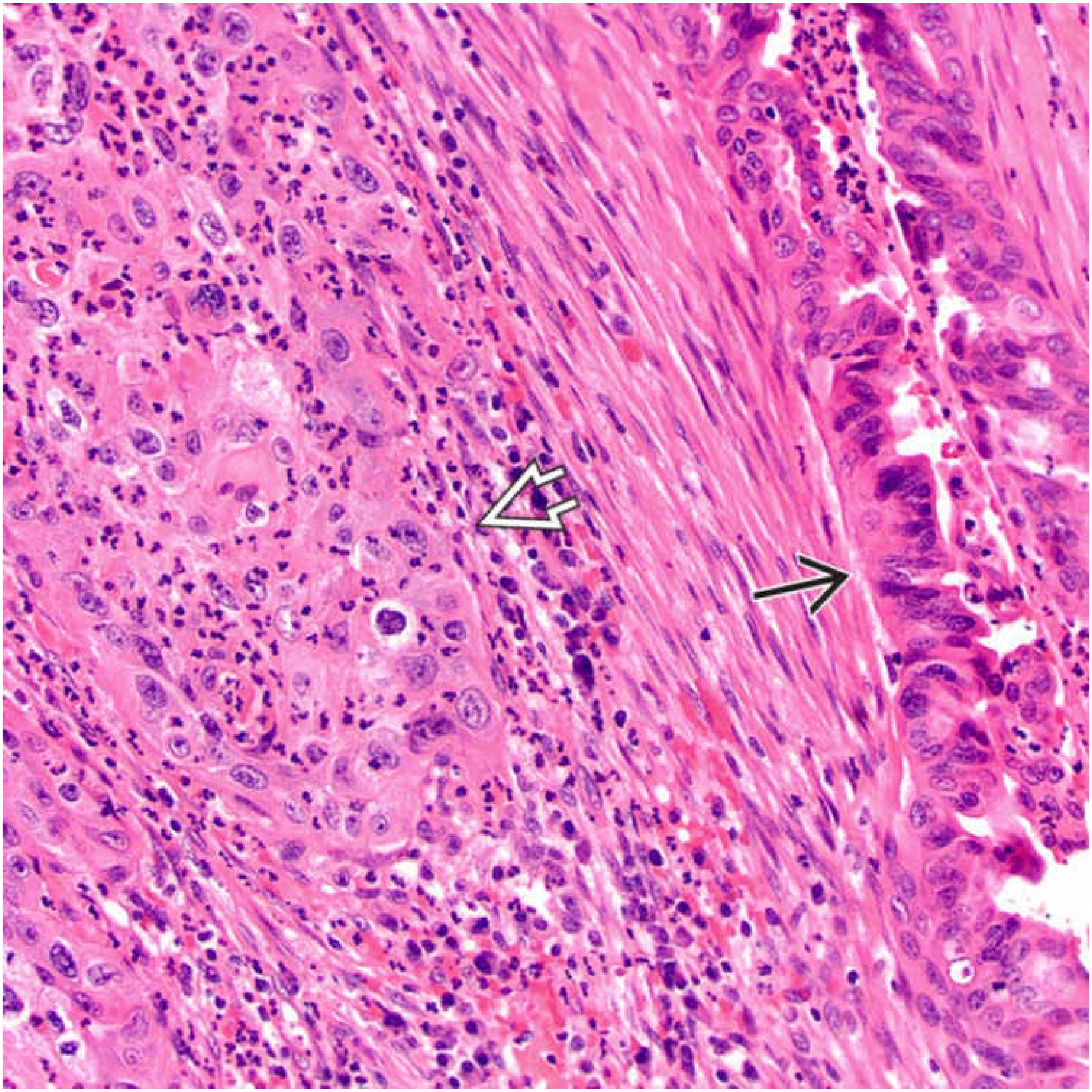


Keratinization
This case of primary squamous cell carcinoma of the gallbladder shows islands of malignant cells with prominent keratinization .



Squamous Metaplasia

The gallbladder mucosa adjacent to invasive squamous cell carcinoma shows a focus of squamous metaplasia with dysplastic changes →. Note that the focus is flanked by preserved gallbladder mucosa showing reactive changes ↷ .



Adenosquamous Carcinoma
This primary adenosquamous carcinoma of the gallbladder shows squamous cell component ⇨ adjacent to a malignant gland → .

TERMINOLOGY

Definitions

- Malignant epithelial neoplasms of gallbladder composed of either pure squamous component or both squamous and glandular components

ETIOLOGY/PATHOGENESIS

Histogenesis

- Neoplastic transformation from squamous metaplasia of gallbladder mucosa
  - Metaplasia → dysplasia → carcinoma sequence
- Progression from preexisting adenocarcinoma
  - Considered "metaplastic carcinoma" like that in breast

Association

- Gallstones present in 40-68% of cases
- Parasitic infestation reported in rare cases

CLINICAL ISSUES

Epidemiology

- Incidence
  - 1-12% of all gallbladder carcinomas
    - Pure squamous cell carcinoma: 0.5-3.0%
- Age
  - Mean age: 65 years (range: 26-89 years)
- Sex
  - Female predominance

Presentation

- Abdominal pain
- Jaundice
- Weight loss
- Palpable abdominal mass

Treatment

- Cholecystectomy ± partial hepatectomy
  - Extended resections may be necessary depending on adjacent organ involvement
  - Resectability rate at diagnosis: ~ 50%
- Chemoradiation therapies may or may not be beneficial

Prognosis

- Overall poor prognosis
  - Median survival: < 1 year
  - Worse than conventional gallbladder adenocarcinoma stage by stage
  - Determined by stage, histologic grade, and ability to achieve R0 resection

IMAGING

General Features

- Help detect gallbladder mass, gallbladder wall thickening, extent of local involvement, nodal and distant metastasis

MACROSCOPIC

General Features

- White-tan, firm or friable, intraluminal fungating mass
  - Most common in fundus
- Diffuse thickening and induration of gallbladder wall
  - May be indistinguishable from cholecystitis
- May involve adjacent organs, including liver, colon, stomach, duodenum, omentum, pancreas, extrahepatic bile ducts, hepatic arteries

MICROSCOPIC

Histologic Features

- Squamous cell carcinoma
  - Composed entirely of squamous component
  - – May show focal or extensive keratinization with keratin pearls and individual cell keratinization
  - – Adjacent gallbladder mucosa may show squamous metaplasia ± dysplasia
  - Spindle cells may predominate in poorly differentiated/sarcomatoid cases
    - – May be confused with high-grade sarcoma
- Adenosquamous carcinoma has both malignant glandular and squamous components
  - Glandular component: Any amount
    - – Similar to conventional gallbladder adenocarcinoma
      - Can be biliary, intestinal, gastric foveolar, or papillary type
  - Squamous component: ≥ 25% of tumor volume
    - – May form separate foci or admixed with glandular component

Cytologic Features

- Proportion of cells with glandular or squamous features varies according to amount in tumor and sampling
- Pure squamous cell carcinoma may be undersampling of adenosquamous carcinoma, and metastatic squamous cell carcinoma must be considered

ANCILLARY TESTS

Histochemistry

- Mucicarmine
  - Help identify intracytoplasmic mucin to confirm presence of glandular component

Immunohistochemistry

- p40, keratin 5/6, p63
  - Positive in squamous component
- CK7, CK19, CEA
  - Positive in glandular component

DIFFERENTIAL DIAGNOSIS

Metastatic Squamous Cell Carcinoma

- Documented history of squamous cell carcinoma in other locations

Adenocarcinoma With Focal Squamous Differentiation

- < 25% squamous component

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Pure squamous cell carcinoma of gallbladder is rare, and metastasis should be ruled out

SELECTED REFERENCES

1. Song, HW, et al. Squamous/adenosquamous carcinoma of the gallbladder: Analysis of 34 cases and comparison of clinicopathologic features and surgical outcomes with adenocarcinoma. *J Surg Oncol*. 2015; 112(6):677–680.
2. Kalayarasan, R, et al. Squamous variant of gallbladder cancer: is it different from adenocarcinoma? *Am J Surg*. 2013; 206(3):380–385.
3. Kim, WS, et al. Clinicopathologic analysis of adenosquamous/squamous cell carcinoma of the gallbladder. *J Surg Oncol*. 2011; 103(3):239–242.
4. Roa, JC, et al. Squamous cell and adenosquamous carcinomas of the gallbladder: clinicopathological analysis of 34 cases identified in 606 carcinomas. *Mod Pathol*. 2011; 24(8):1069–1078.
5. Chan, KM, et al. Adenosquamous/squamous cell carcinoma of the gallbladder. *J Surg Oncol*. 2007; 95(2):129–134.

Neuroendocrine Tumors of Gallbladder

KEY FACTS

Terminology

- Neoplasms with neuroendocrine differentiation
  - Well-differentiated neuroendocrine neoplasm (WDNEN): Grades 1 and 2
  - Poorly differentiated neuroendocrine carcinoma (PDNC): Grade 3
  – Small cell carcinoma, large cell neuroendocrine carcinoma

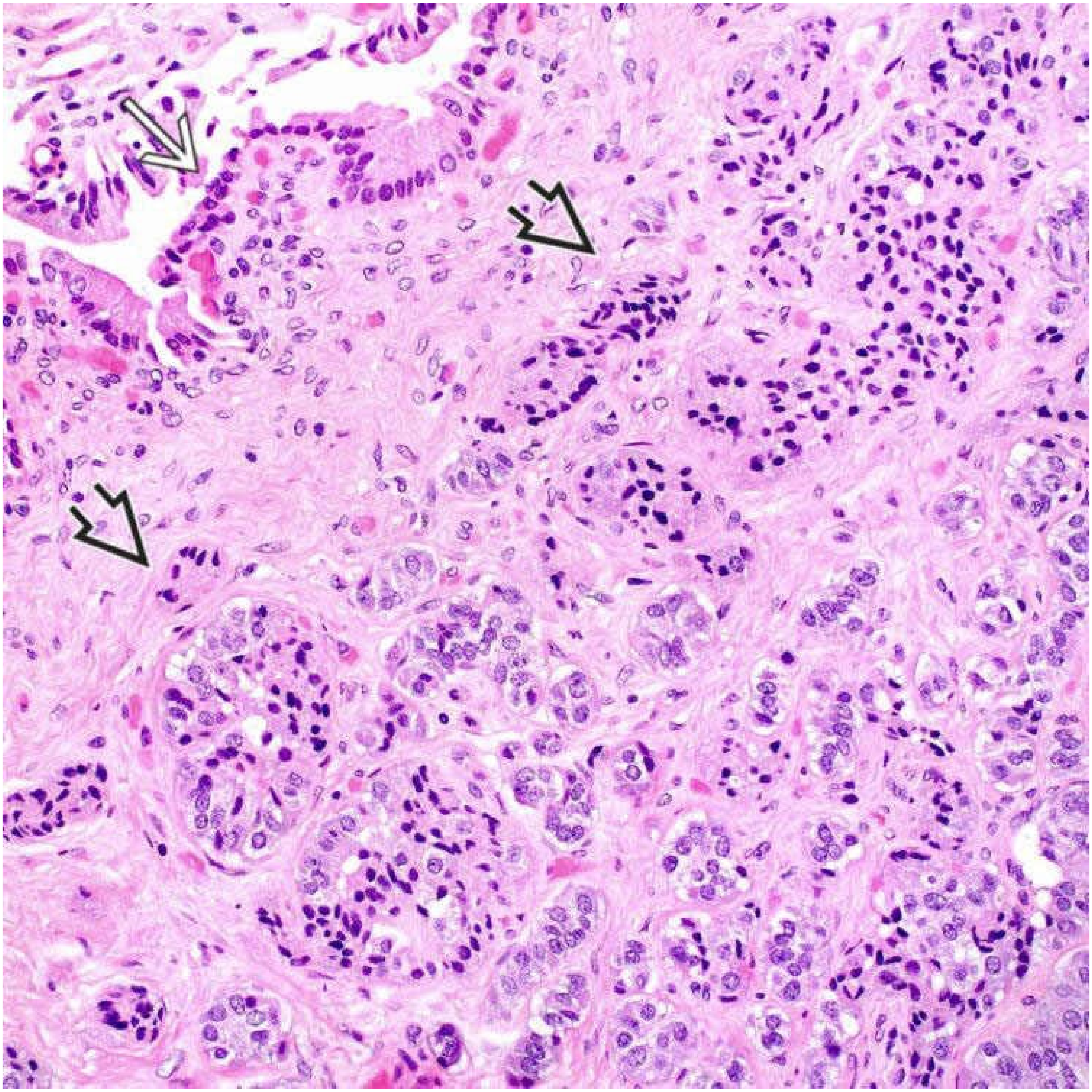
Clinical Issues

- WDNEN: All tumors have potential to metastasize
- PDNC: Dismal prognosis

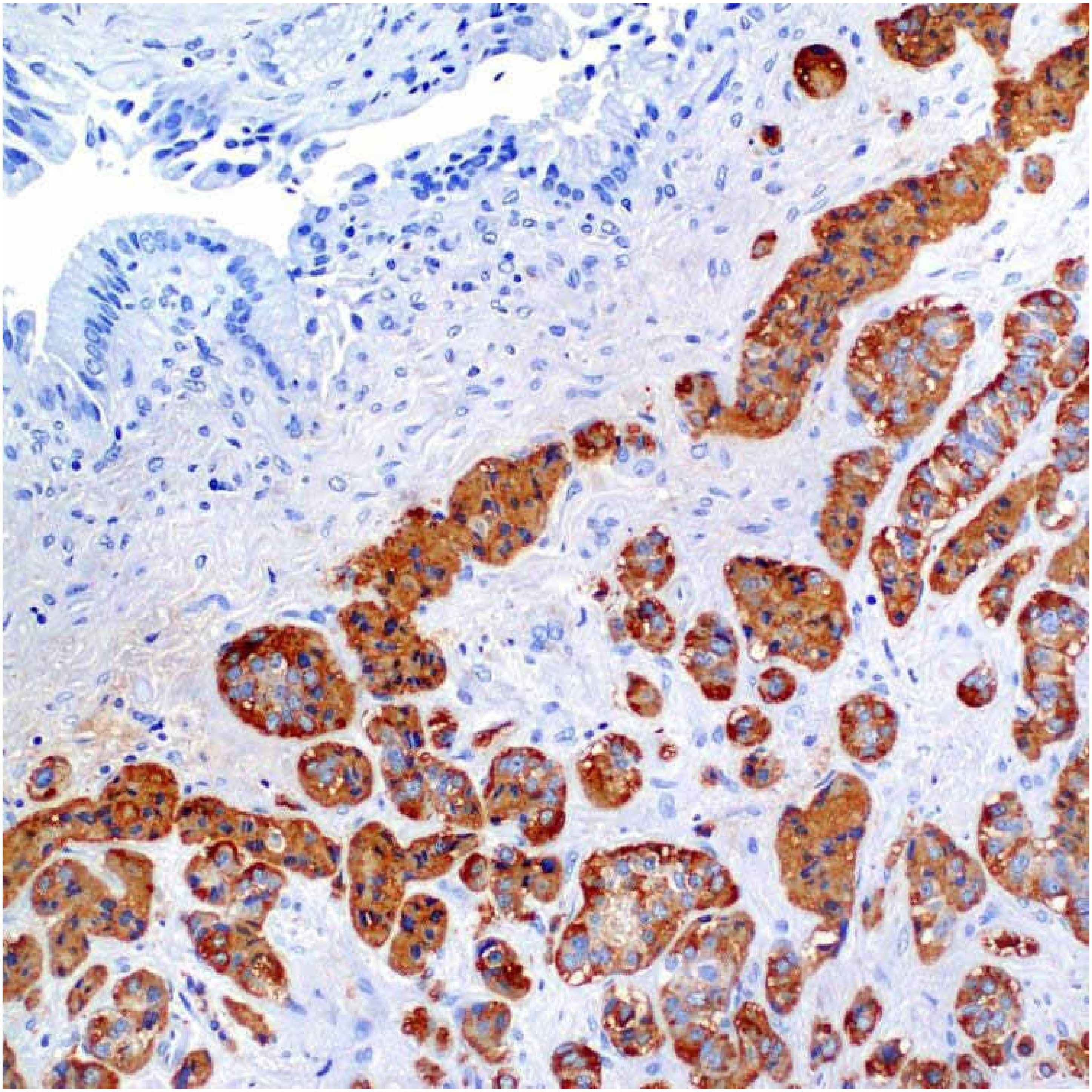
Microscopic

- WDNEN
  - Uniform round nuclei with minimal nuclear atypia
  - Finely stippled (“salt and pepper”) chromatin
  - Variable mitotic activity, but < 20 per 10 HPF
  - No or minimal necrosis
- Small cell carcinoma
  - Small, round or fusiform hyperchromatic nuclei
  - Finely dispersed granular chromatin
  - Nuclear moulding
  - High mitotic rate
  - Often show extensive necrosis &/or frequent apoptotic bodies
- Large cell neuroendocrine carcinoma
  - Large polygonal cells
  - Nucleoli are often present and may be prominent
  - Variable amounts of cytoplasm but usually abundant
  - Frequent necrosis
- Grading by mitotic rate and Ki-67 labeling index
  - Grade 1 (low grade): Mitosis < 2 per 10 HPF and Ki-67 < 3%

- Grade 2 (intermediate grade): Mitosis 2-20 per 10 HPF &/or Ki-67 3-20%
- Grade 3 (high grade): Mitosis > 20 per 10 HPF &/or Ki-67 > 20%

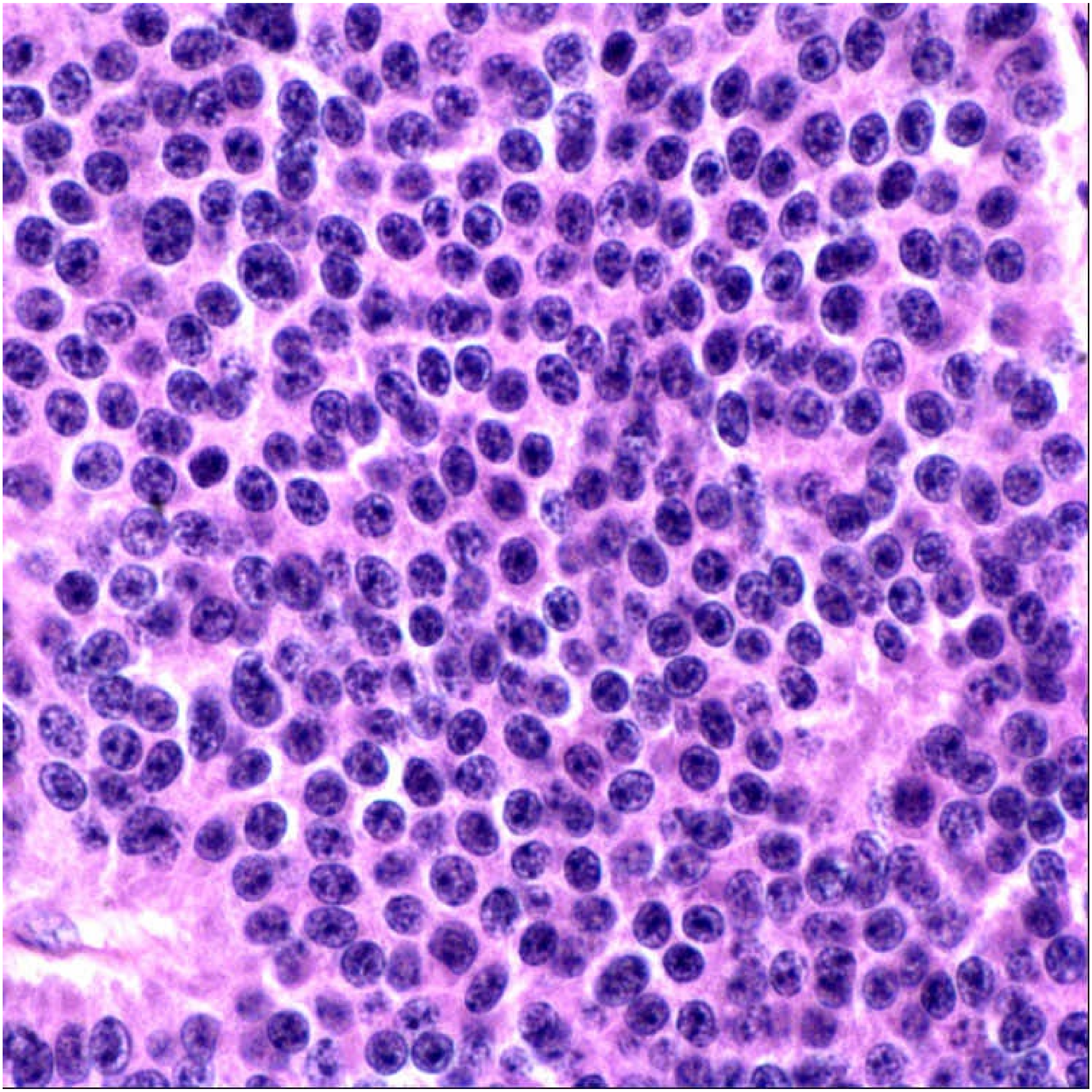


Incidental Well-Differentiated Neuroendocrine Neoplasm
This 3-mm, low-grade well-differentiated neuroendocrine neoplasm (WDNEN) (carcinoid) ➪ was incidentally found at the gallbladder neck. Cholecystectomy was performed for cholelithiasis. The overlying gallbladder mucosa ⇒ appears unremarkable.



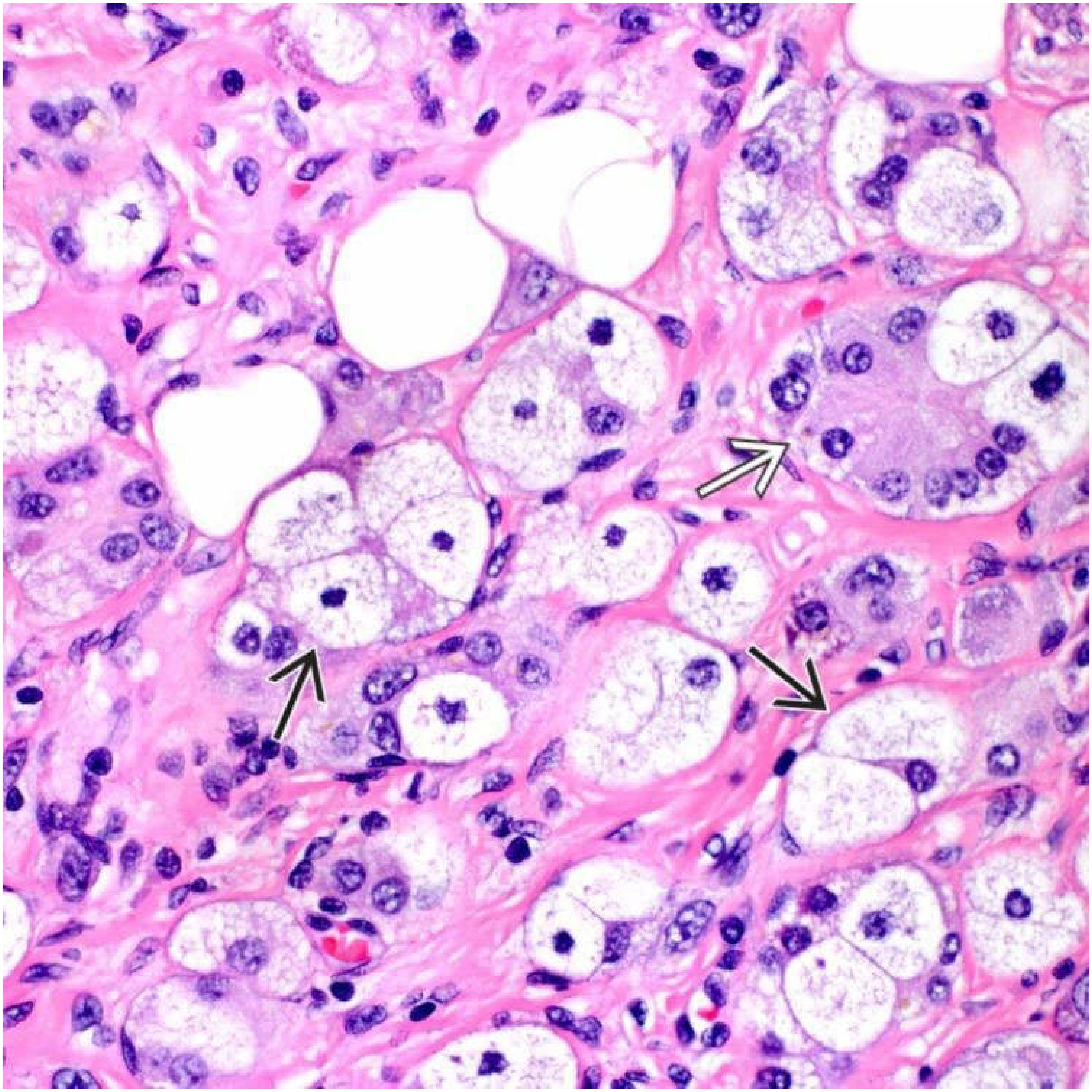
Nested Growth Pattern

Tumor cells of this gallbladder WDNEN show diffuse cytoplasmic immunoreactivity to antichromogranin antibody, which highlights a nested growth pattern. Same staining results are also observed for synaptophysin.



Histologic Features

Tumor cells of WDNEN typically have uniform round nuclei, finely stippled (“salt and pepper”) chromatin, inconspicuous nucleoli, and eosinophilic cytoplasm. No mitotic figures or necrosis are seen in this microphotograph.



Clear Cell Variant
This WDNEN shows nested tumor cells, the majority of which have abundant foamy cytoplasm due to lipid accumulation →. Tumor cells with eosinophilic cytoplasm are also present ⇒ .

TERMINOLOGY

Abbreviations

- Well-differentiated neuroendocrine neoplasm (WDNEN)
- Poorly differentiated neuroendocrine carcinoma (PDNC)

Synonyms

- WDNEN
    - Well-differentiated neuroendocrine tumor
    - Carcinoid tumor (not preferred)
- PDNC
    - Small cell carcinoma
        - – Small cell neuroendocrine carcinoma
        - – Small cell undifferentiated carcinoma
        - – Oat cell carcinoma
    - Large cell neuroendocrine carcinoma
    - High-grade neuroendocrine carcinoma

Definitions

- Neoplasms with neuroendocrine differentiation arising in gallbladder, including WDNEN and PDNC

ETIOLOGY/PATHOGENESIS

Disease Association

- PDNC is frequently associated with gallstones
- WDNEN is infrequently associated with von Hippel-Lindau disease and multiple endocrine neoplasia type 1

CLINICAL ISSUES

Epidemiology

- Incidence
    - 0.2-0.3 per 100,000 population
    - – WDNEN: 0.2% of all sites
    - – PDNC: 4.0% of all gallbladder malignancies
    - □ Small cell carcinoma > large cell
- Age
    - Older adults, usually 6th-7th decades of life
        - – Range: 25-85 years
- Sex
    - Slightly more common in females

Presentation

- WDNEN: Usually asymptomatic
    - Incidental finding after cholecystectomy for cholelithiasis or cholecystitis in most cases
    - Abdominal pain in occasional cases
    - Not typically associated with carcinoid syndrome
- PDNC: Similar to other types of gallbladder carcinoma

- Abdominal pain, jaundice, palpable abdominal mass
- Rare cases of ectopic hormone production giving rise to Cushing syndrome or paraneoplastic neuropathy
- May be incidental finding at time of cholecystectomy for cholelithiasis or cholecystitis

Treatment

- Surgical approaches
  - Cholecystectomy
  - Extended resection, including hepatic lobectomy and regional lymph node dissection, may be necessary depending on extent of disease
- Chemotherapy for PDNC
  - Small cell carcinoma is highly sensitive
- Role of radiotherapy remains undefined

Prognosis

- WDNEN: All tumors have potential to metastasize
  - Tumors > 2.0 cm are more likely to metastasize and to extend into liver
  - Tumors < 0.5 cm usually do not metastasize
  - Overall 5-year survival rate: 41% (according to SEER data)
- PDNC: Dismal
  - 40-50% of cases have disseminated disease at time of diagnosis
  - Many patients die within 6 months

IMAGING

General Features

- Help detect gallbladder mass, wall thickening, extent of local involvement, nodal and distant metastasis
  - WDNEN may be difficult to detect, mainly because of small size
  - – Octreotide scan may be helpful

MACROSCOPIC

General Features

- Can arise in any portion of gallbladder: Fundus, body, or neck
  - WDNEN
  - Nodular or polypoid lesion, generally < 2 cm
  - Cut surface is usually solid, homogeneous, grey-white or yellow
  - Rarely multiple
- PDNC
  - Range from diffuse thickening of gallbladder wall to mass lesion

MICROSCOPIC

Histologic Features

- WDNEN
  - Growth patterns
  - – Nested, trabecular, insular, tubular/glandular, cribriform
- Uniform round nuclei with minimal nuclear atypia
- – Finely stippled ("salt and pepper") chromatin
- – Inconspicuous nucleoli
- – Moderate amounts of eosinophilic granular cytoplasm
- – Variable mitotic activity but < 20 per 10 HPF
- No or minimal necrosis
- Overlying mucosa is usually intact and may show hyperplastic change
- Clear cell variant
- – Characterized by abundant foamy cytoplasm containing small lipid vacuoles
- – Either sporadic or associated with von Hippel-Lindau disease
- Small cell carcinoma
  - Growth patterns
    - – Solid sheets, nests, ribbons, rosettes, rarely tubules
    - – Palisading may be prominent at periphery of tumor nests
  - Small, round or fusiform hyperchromatic nuclei
    - – Finely dispersed granular chromatin
    - – Inconspicuous nucleoli
    - – Scant eosinophilic cytoplasm
    - – Nuclear moulding
    - – High mitotic rate
  - Often show extensive necrosis &/or frequent apoptotic bodies
    - – Viable tumor cells may be limited to perivascular areas
    - – Vessel walls may show deeply basophilic DNA deposition from necrotic tumor cells (Azzopardi effect)
  - Focal areas (< 30%) of squamous or glandular differentiation may be seen
  - Overlying mucosa may be ulcerated or dysplastic
    - – Subepithelial tumor growth is common
- Large cell neuroendocrine carcinoma
  - Growth patterns
    - – Nested, trabecular, rosettes
      - Peripheral palisading may be seen
  - Large polygonal cells
    - – Vesicular nuclei

    - Nucleoli are often present and may be prominent
    - Variable amounts of cytoplasm but usually abundant
    - High mitotic rate
  - Frequent necrosis
- Mixed adenoneuroendocrine carcinoma
  - Composed of intermingled adenocarcinoma or squamous cell carcinoma with PDNC or WDNEN
    - Each component is ≥ 30% of tumor volume

Grading by Mitotic Rate and Ki-67 Labeling Index

- Grade 1 (low grade): Mitosis < 2 per 10 HPF and Ki-67 < 3%
  - WDNEN
- Grade 2 (intermediate grade): Mitosis 2-20 per 10 HPF &/or Ki-67 3-20%
  - WDNEN
- Grade 3 (high grade): Mitosis > 20 per 10 HPF &/or Ki-67 > 20%
  - Small cell carcinoma (average Ki-67 index: 70-90%)
  - Large cell neuroendocrine carcinoma
  - Non-small, non-large cell high-grade neuroendocrine carcinoma
    - Morphologically similar to WDNEN but Ki-67 labeling index > 20%
- Recommendation
  - Mitotic rate: Counting 50 high-power (40x) fields in areas with highest mitotic activity
  - Ki-67 index: Counting 500-2000 tumor cells in areas with highest nuclear labeling

ANCILLARY TESTS

Immunohistochemistry

- Positive for neuroendocrine markers synaptophysin, chromogranin, CD56
  - Small cell carcinoma can be negative for these markers
  - Morphology is more important than immunophenotype for diagnosis

○ Positive stains can be focal, weak, or show cytoplasmic fine granules

– Particularly true of chromogranin

- Positive for pankeratin
  - Paranuclear dot-like staining pattern is seen in a small subset of small cell carcinomas
- May be positive for TTF-1
- von Hippel-Lindau disease-associated WDNEN may be positive for inhibin

DIFFERENTIAL DIAGNOSIS

WDNEN vs. PDNC

- Crucial distinction since behaviors and treatment options are different
- Separated by mitotic rate, Ki-67 labeling index, and cytomorphologic features

Well-Differentiated Adenocarcinoma

- Tubular formation in WDNEN may be confused with conventional adenocarcinoma
  - Neuroendocrine markers are helpful
- Focal neuroendocrine differentiation is not uncommon in conventional adenocarcinoma
  - Stains for neuroendocrine markers usually show scattered positive cells rather than diffuse positivity

Undifferentiated Carcinoma

- May be small cell (nonneuroendocrine) or spindle cell predominant
- Giant cells, including osteoclast-like giant cells, are often present
- Poorly formed glandular structures may be seen
- Negative for neuroendocrine markers

Metastatic Neuroendocrine Tumor/Carcinoma

- Documented history of neuroendocrine tumor/carcinoma in other locations
- Imaging studies can be helpful

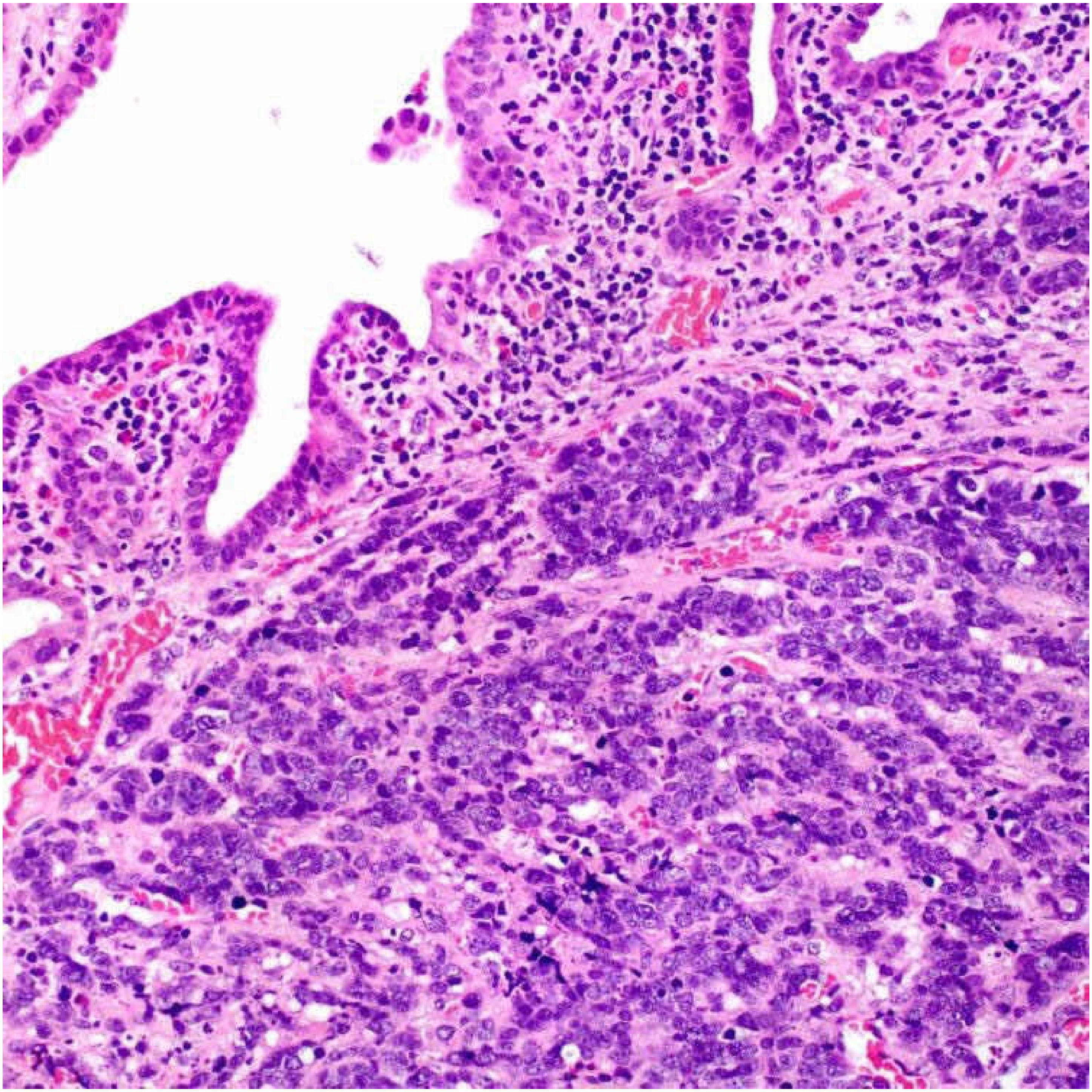
Lymphoma

- Crucial distinction since behaviors and treatment options are different
- Immunostains for lymphoid and neuroendocrine markers are helpful

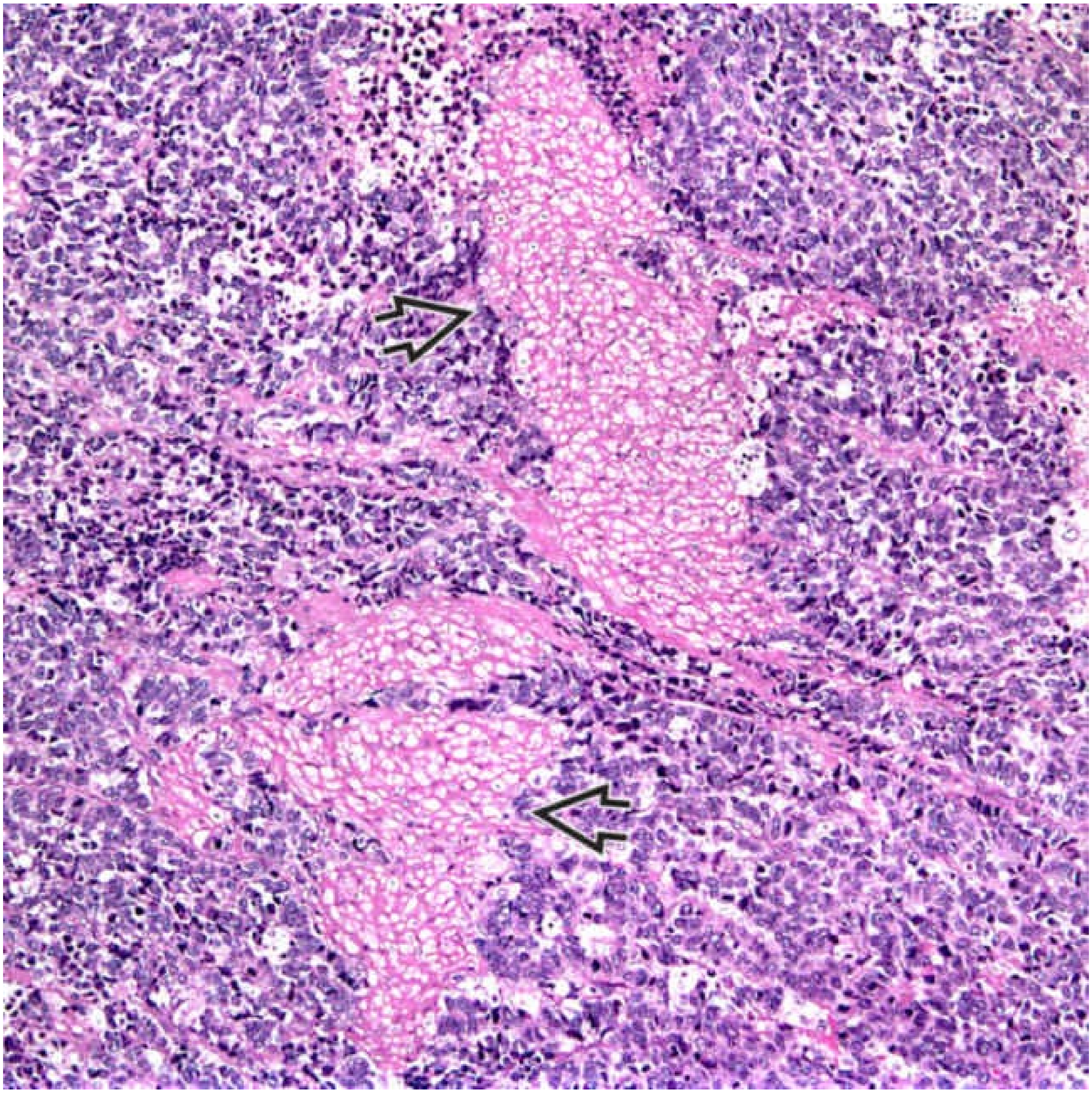
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Carcinoid tumor: Correlation between immunohistochemical expression of peptide hormones and serologic levels has not been determined
- PDNC: Important to diagnose this subtype so that patients get correct chemotherapy

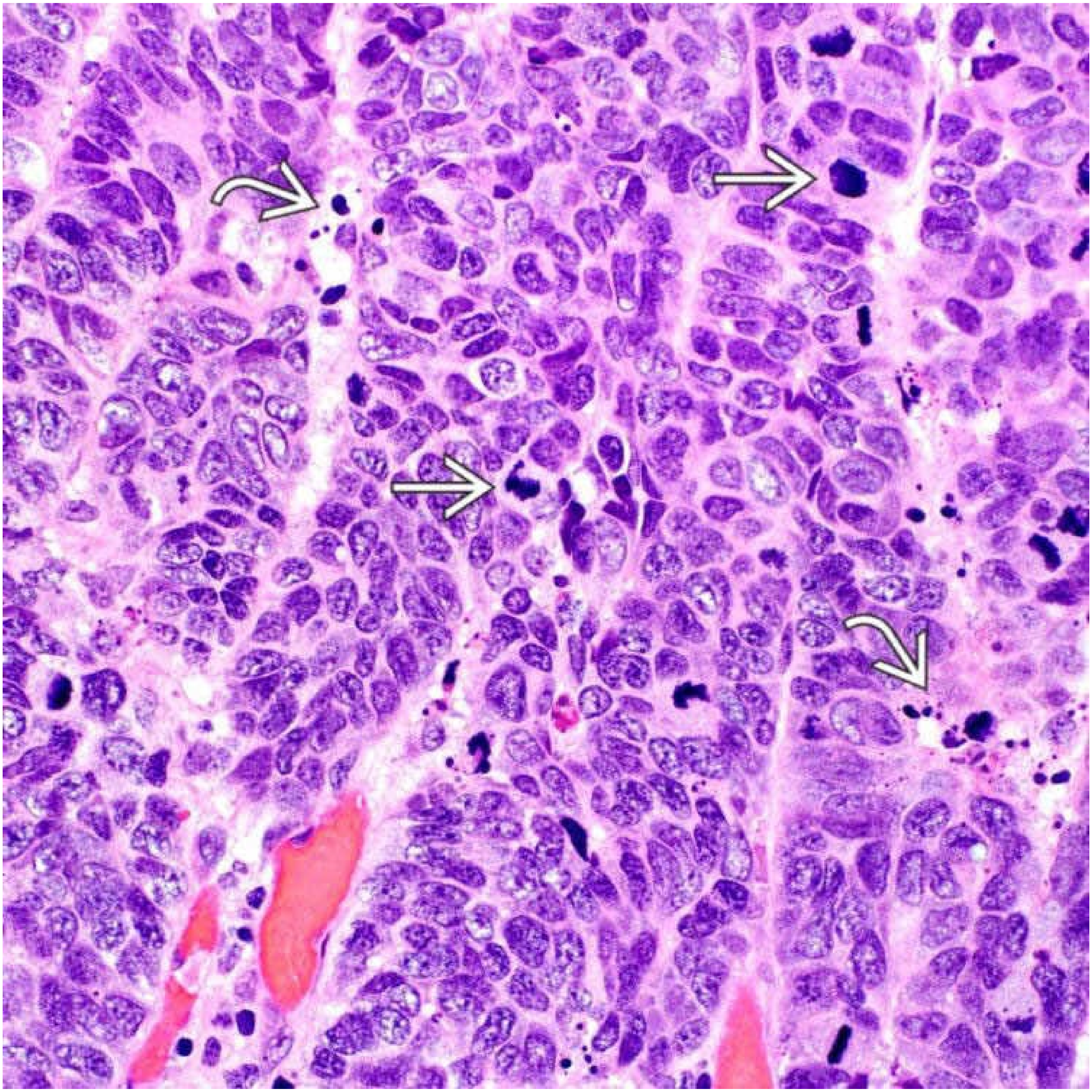


Small Cell Carcinoma
This case of gallbladder small cell carcinoma shows a characteristic subepithelial growth pattern. Nuclear hyperchromasia of tumor cells is evident at this power.



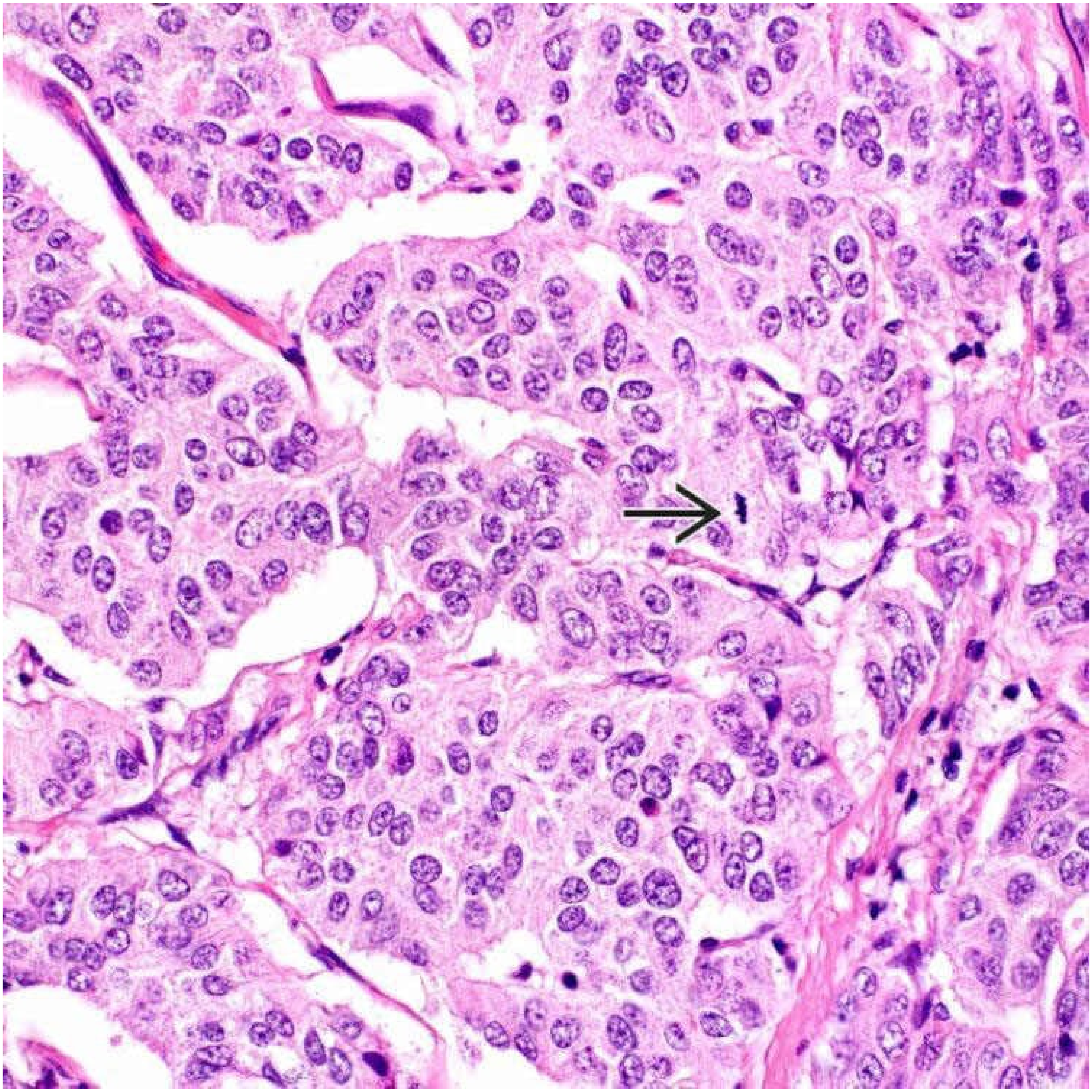
Tumor Necrosis

This case of gallbladder small cell carcinoma shows sheets of small hyperchromatic tumor cells. Foci of tumor necrosis ➯ are present, which can be more extensive and grossly prominent in some cases.

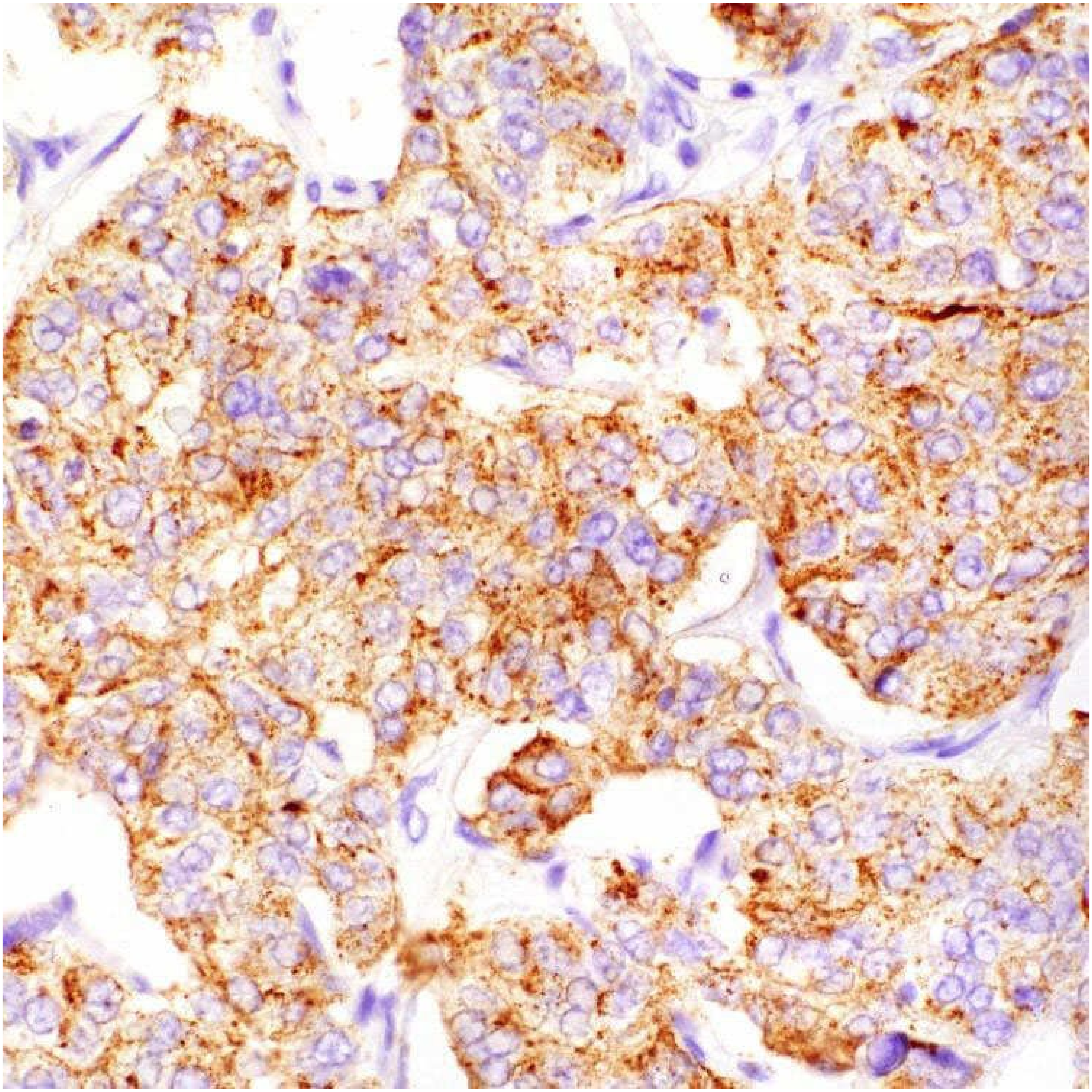


High Mitotic Rate

Tumor cells in this case of gallbladder small cell carcinoma are predominantly fusiform and arranged in a trabecular pattern. Numerous mitotic figures ⇒ and apoptotic bodies ⇒ are seen.

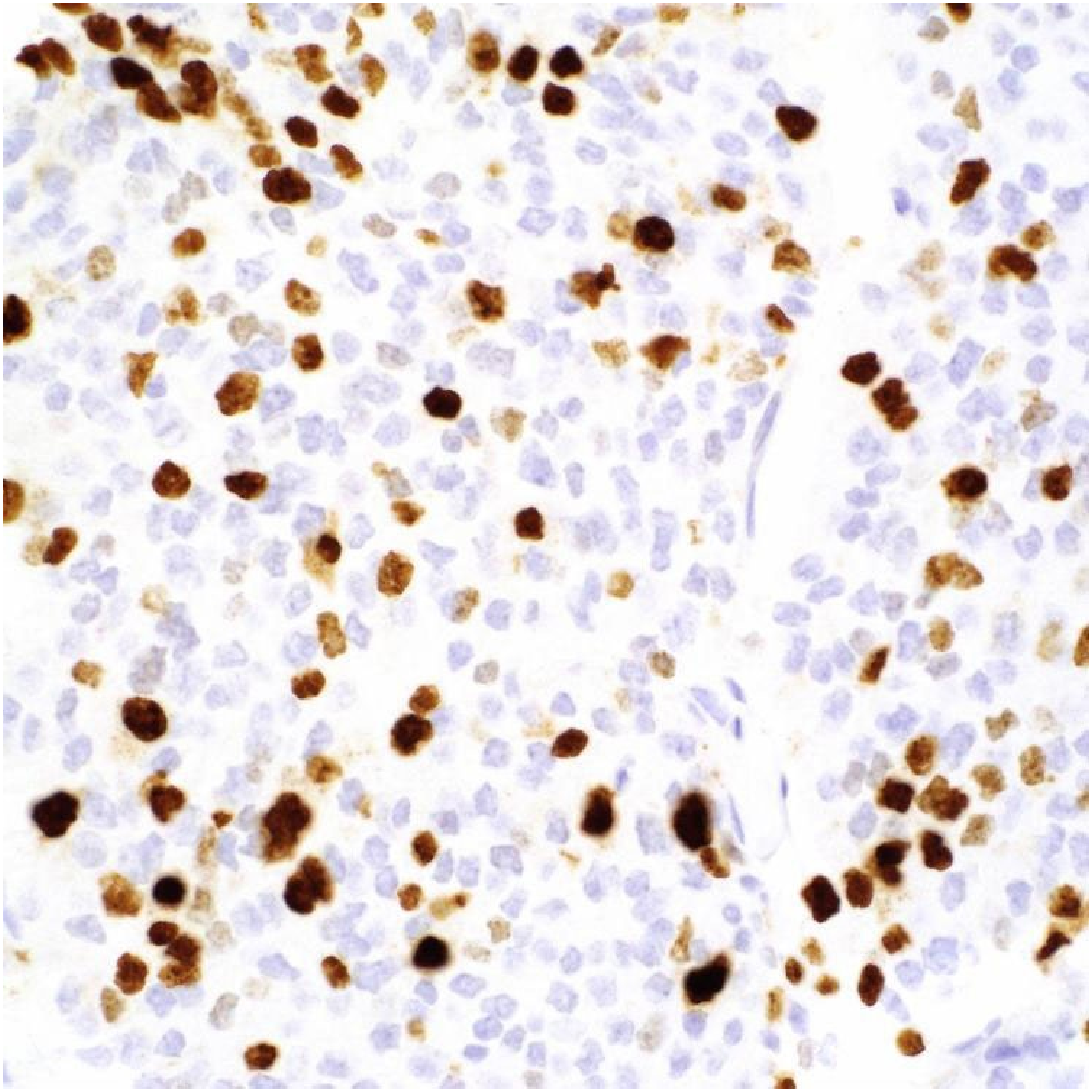


Well-Differentiated Morphology
This gallbladder tumor shows sheets and trabeculae of cells with uniform round nuclei, inconspicuous nucleoli, and moderate amounts of eosinophilic cytoplasm. Only rare mitoses → are identified. The histologic findings are consistent with WDNEN.



Chromogranin Immunostain

Tumor cells are positive for neuroendocrine markers synaptophysin and chromogranin by immunohistochemistry. Shown in this microphotograph is chromogranin immunostain characterized by cytoplasmic fine granules.



High Ki-67 Labeling Index
Immunostain for Ki-67 shows a labeling index of ~ 50%. The tumor is thus qualified for high-grade neuroendocrine carcinoma despite the histologic features that are not typical of small cell or large cell neuroendocrine carcinoma.

SELECTED REFERENCES

1. Adachi, T, et al. Gallbladder small cell carcinoma: a case report and literature review. *Surg Case Rep*. 2016; 2(1):71.
2. Buscemi, S, et al. “Pure” large cell neuroendocrine carcinoma of the gallbladder. report of a case and review of the literature. *Int J Surg*. 2016; 28(Suppl 1):S128–S132.
3. Koizumi, M, et al. Carcinoid tumor of the gallbladder: report of two cases. *Clin J Gastroenterol*. 2011; 4(5):323–330.

4. Albores-Saavedra, J, et al. Carcinoid tumors and small-cell carcinomas of the gallbladder and extrahepatic bile ducts: a comparative study based on 221 cases from the Surveillance, Epidemiology, and End Results Program. *Ann Diagn Pathol*. 2009; 13(6):378–383.

Granular Cell Tumor

KEY FACTS

Terminology

- Benign tumor with schwannian differentiation
  - Most common nonepithelial tumor of extrahepatic bile ducts

Clinical Issues

- Occur most often in young African American women
  - Mean age: 34.7 years
- Most frequent location is common bile duct
- Often discovered incidentally
- Cured by adequate surgical excision
  - Excellent prognosis
  - Malignant granular cell tumors (GCTs) not reported in biliary tract

Macroscopic

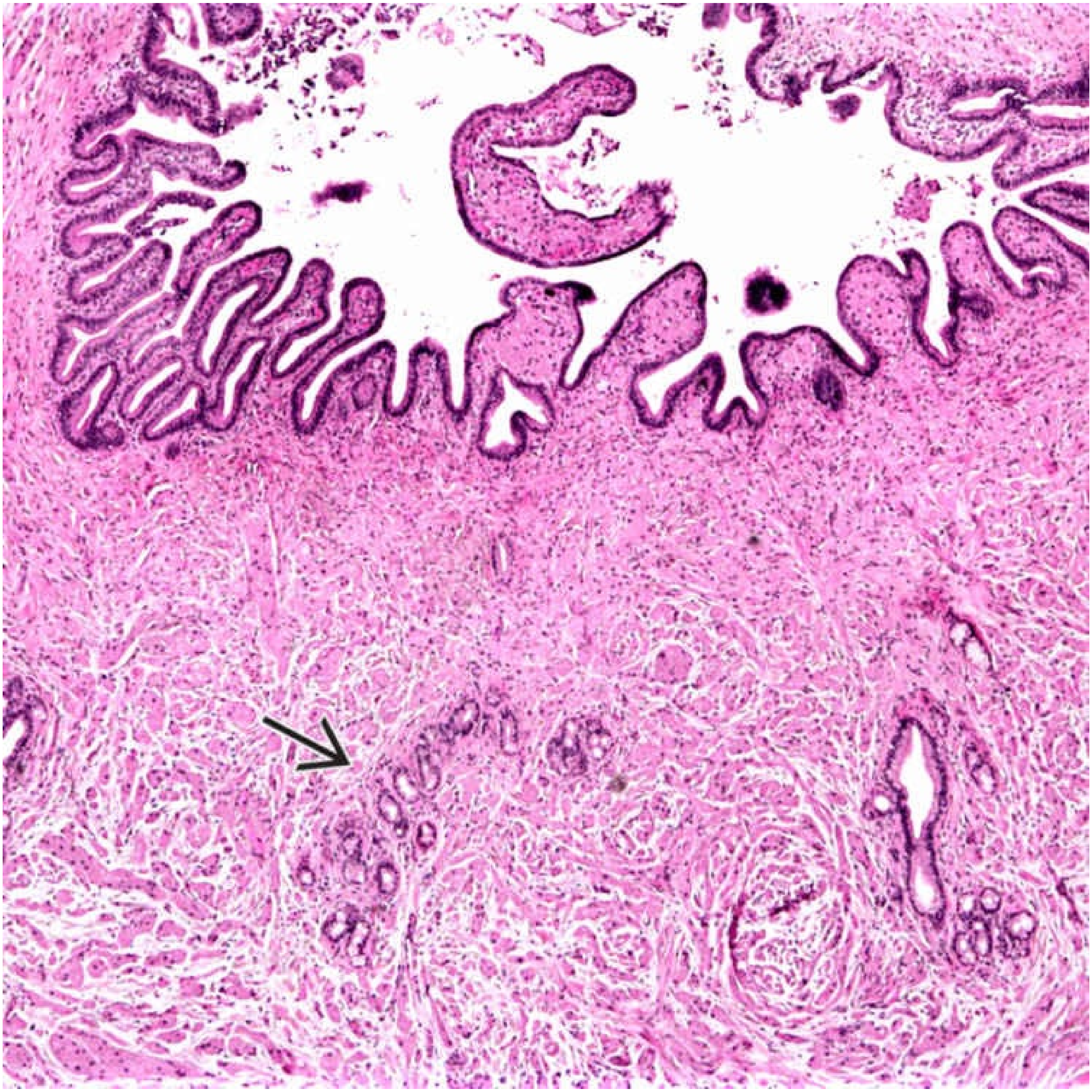
- Often grows concentrically around bile duct, compressing lumen
- Usually < 3 cm in greatest dimension

Microscopic

- Nests or sheets of infiltrating cells
  - Cells may be separated by collagenous bands
  - Oval to polygonal cells
  - Abundant pink granular cytoplasm with small hyperchromatic nuclei
- Can be associated with marked atypia of overlying biliary surface epithelium
  - May mimic malignancy
  - Important to recognize underlying GCT

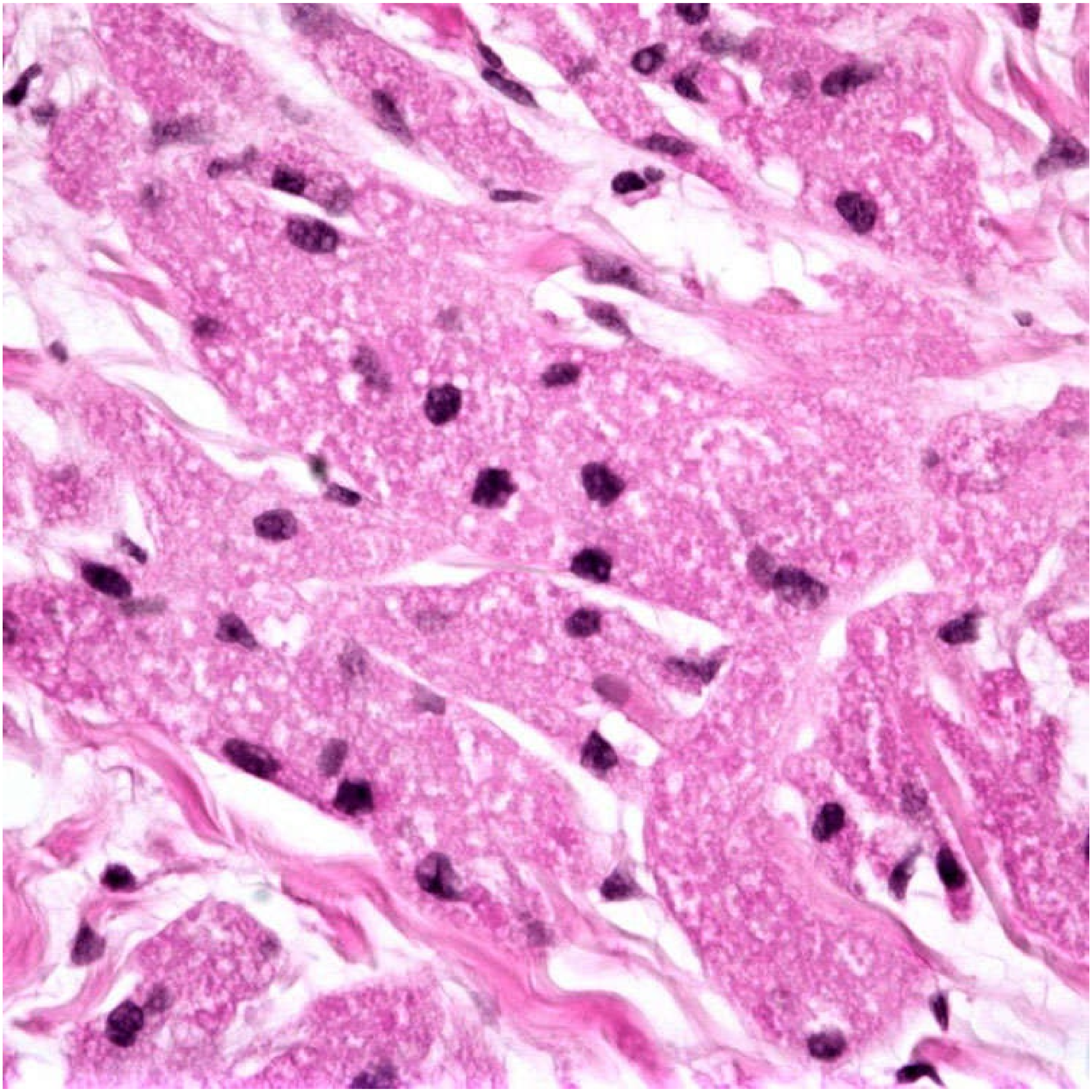
Ancillary Tests

• Strong diffuse immunopositivity with S100

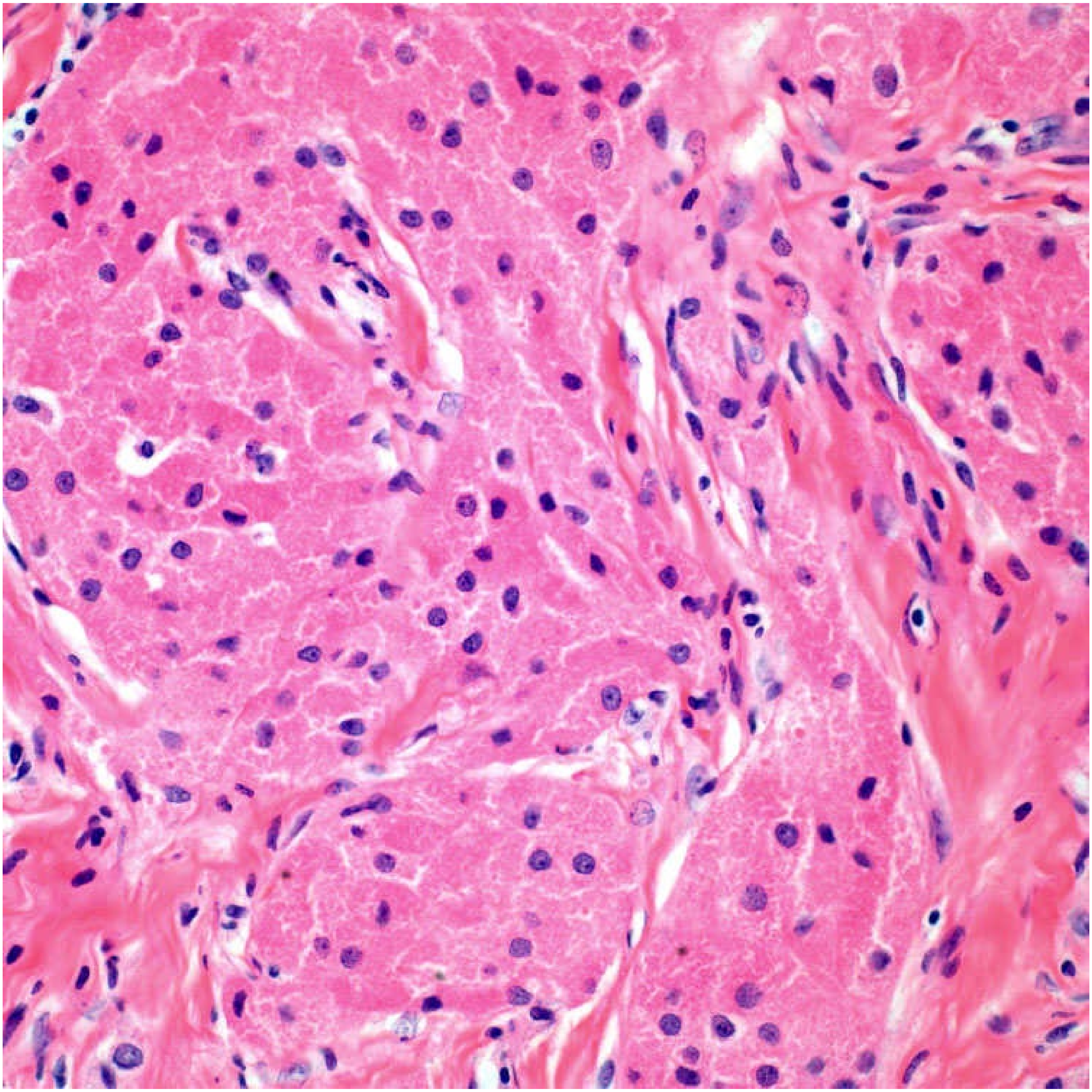


Concentric Growth Pattern

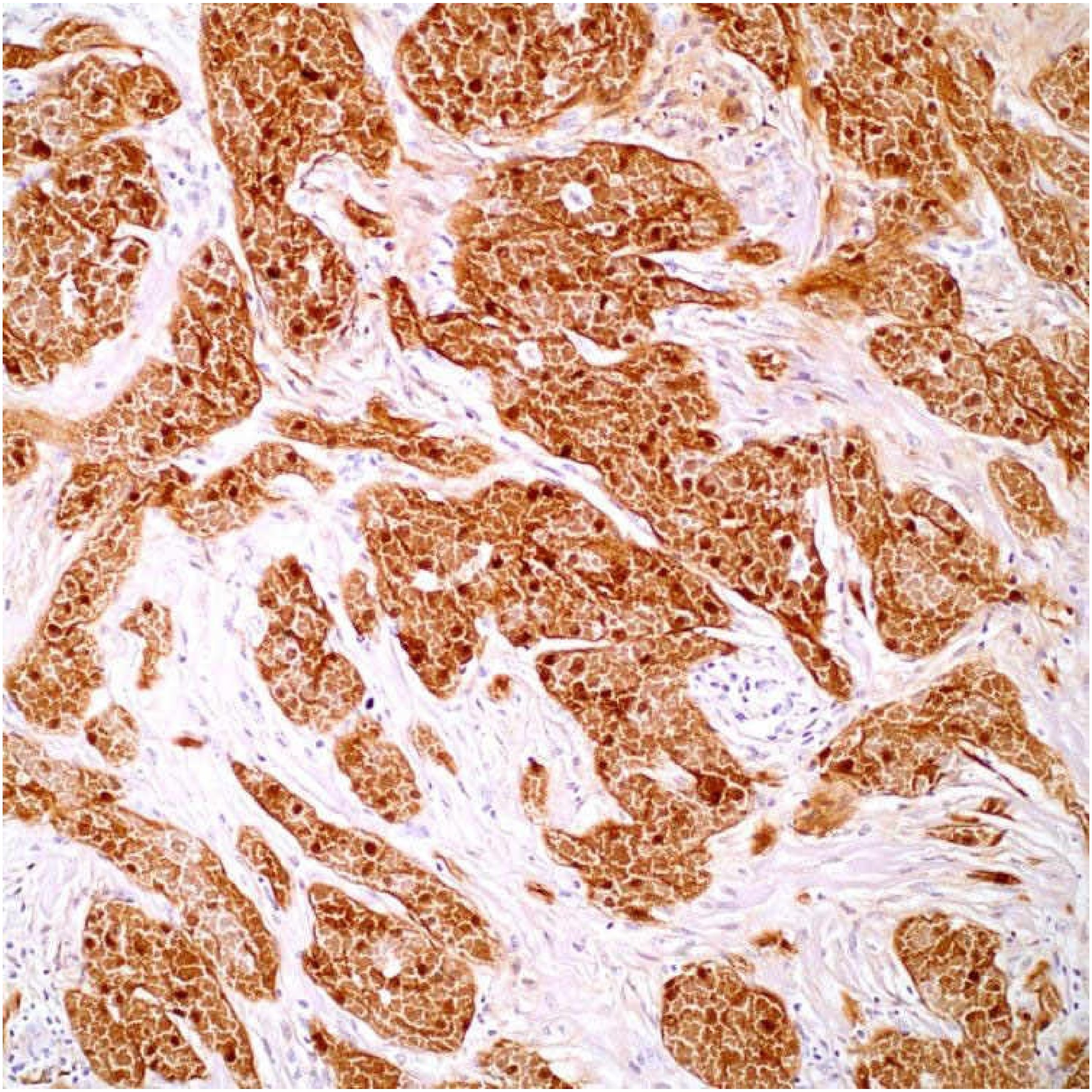
This granular cell tumor is growing concentrically around the common bile duct, compressing the lumen. The tumor cells can have a very infiltrative growth pattern and may surround small peribiliary glands → .



Granular Cytoplasm
The tumor cells have abundant pink granular cytoplasm and small hyperchromatic nuclei.



Interspersed Collagen Bands
The granular, pink, polygonal tumor cells are often interspersed with bands of collagen.



S100

S100 is strongly and diffusely positive within tumor cells. (Courtesy J. McKenney, MD.)

TERMINOLOGY

Abbreviations

- Granular cell tumor (GCT)

Synonyms

- Granular cell myoblastoma

Definitions

- Benign tumor composed of large, granular, eosinophilic cells
  - Immunohistochemistry and electron microscopy have shown schwannian differentiation
- Most common nonepithelial tumor of extrahepatic bile ducts

CLINICAL ISSUES

Epidemiology

- Age
  - Young patients
    - Mean: 34.7 years; range: 11-61 years
- Sex
  - More common in women
- Ethnicity
  - More common in African Americans

Site

- Occurs most frequently in common bile duct
  - Majority of tumors at or near confluence of cystic (37%), hepatic (15%), and common bile ducts (50%)
  - Rarely (4%) involves gallbladder
- May be multicentric

Presentation

- Common bile duct or hepatic duct tumors typically present with obstructive signs/symptoms
  - Jaundice
  - Hepatomegaly
  - Right upper quadrant pain
- Cystic duct tumors more often present with biliary colic, occasionally cholecystitis
- Often discovered incidentally

Treatment

- Cured by adequate surgical excision
  - Usually amenable to simple excision
  - Recurrence rare

Prognosis

- Benign; malignant GCT have not been documented in the biliary tract

IMAGING

General Features

- Ultrasound, percutaneous transhepatic cholangiography, or endoscopic retrograde cholangiopancreatography may be useful
    - May mimic cholangiocarcinoma or sclerosing cholangitis radiographically

MACROSCOPIC

General Features

- Firm, yellow-tan to yellow-white, ill-defined mass
    - Often grows concentrically around bile duct, compressing lumen
- Usually < 3 cm in greatest dimension

MICROSCOPIC

Histologic Features

- Nests or sheets of cells infiltrating soft tissue
    - Cells may be separated by collagenous bands
    - – Older lesions may contain more connective tissue than tumor cells
- May cluster around or infiltrate peripheral nerves
- Large oval to polygonal cells
    - Abundant acidophilic (pink) granular cytoplasm with occasional globules
    - Small hyperchromatic nuclei
    - Occasionally, spindled granular cells may be seen
- May be associated with marked proliferation and atypia of overlying biliary surface epithelium
    - Epithelial reaction can mimic dysplasia or carcinoma

ANCILLARY TESTS

Immunohistochemistry

- Immunoreactivity with S100, CD68, myelin proteins, and inhibin

DIFFERENTIAL DIAGNOSIS

Cholangiocarcinoma

- GCT may have striking associated overlying epithelial cell proliferation with atypia
- Important to recognize underlying associated GCT and lack of invasive glandular component

Rhabdomyoma

- Pediatric patients
- Cells have cross striations, lack granular cytoplasm

Sclerosing Cholangitis

- GCT can mimic sclerosing cholangitis radiographically
- Histologic appearance of sclerosing cholangitis very different from GCT

Leiomyoma

- Spindled cells with fascicular growth pattern
- Positive smooth muscle markers, negative S100

SELECTED REFERENCES

1. Patel, AJ, et al. Granular cell tumor of the biliary tract. *Gastroenterol Hepatol (N Y)*. 2010; 6(5):331–336.
2. Karakozis, S, et al. Granular cell tumors of the biliary tree. *Surgery*. 2000; 128(1):113–115.
3. te Boekhorst, DS, et al. Granular cell tumor at the hepatic duct confluence mimicking Klatskin tumor. A report of two cases and a review of the literature. *Dig Surg*. 2000; 17(3):299–303.
4. Butler, JD, Jr., et al. Granular cell tumor of the extrahepatic biliary tract. *Am Surg*. 1998; 64(11):1033–1036.
5. Eisen, RN, et al. Granular cell tumor of the biliary tree. A report of two cases and a review of the literature. *Am J Surg Pathol*. 1991; 15(5):460–465.

Embryonal Rhabdomyosarcoma

KEY FACTS

Clinical Issues

- Most frequently described in children, in extrahepatic biliary tree
  - 1% of all rhabdomyosarcomas occurring in children
  - Most common malignant neoplasm of extrahepatic biliary tree in children
- Occasionally seen in adults, usually in gallbladder
- Long-term survival can be achieved with modern multimodality therapy
  - Estimated 5-year survival rate: 66%

Macroscopic

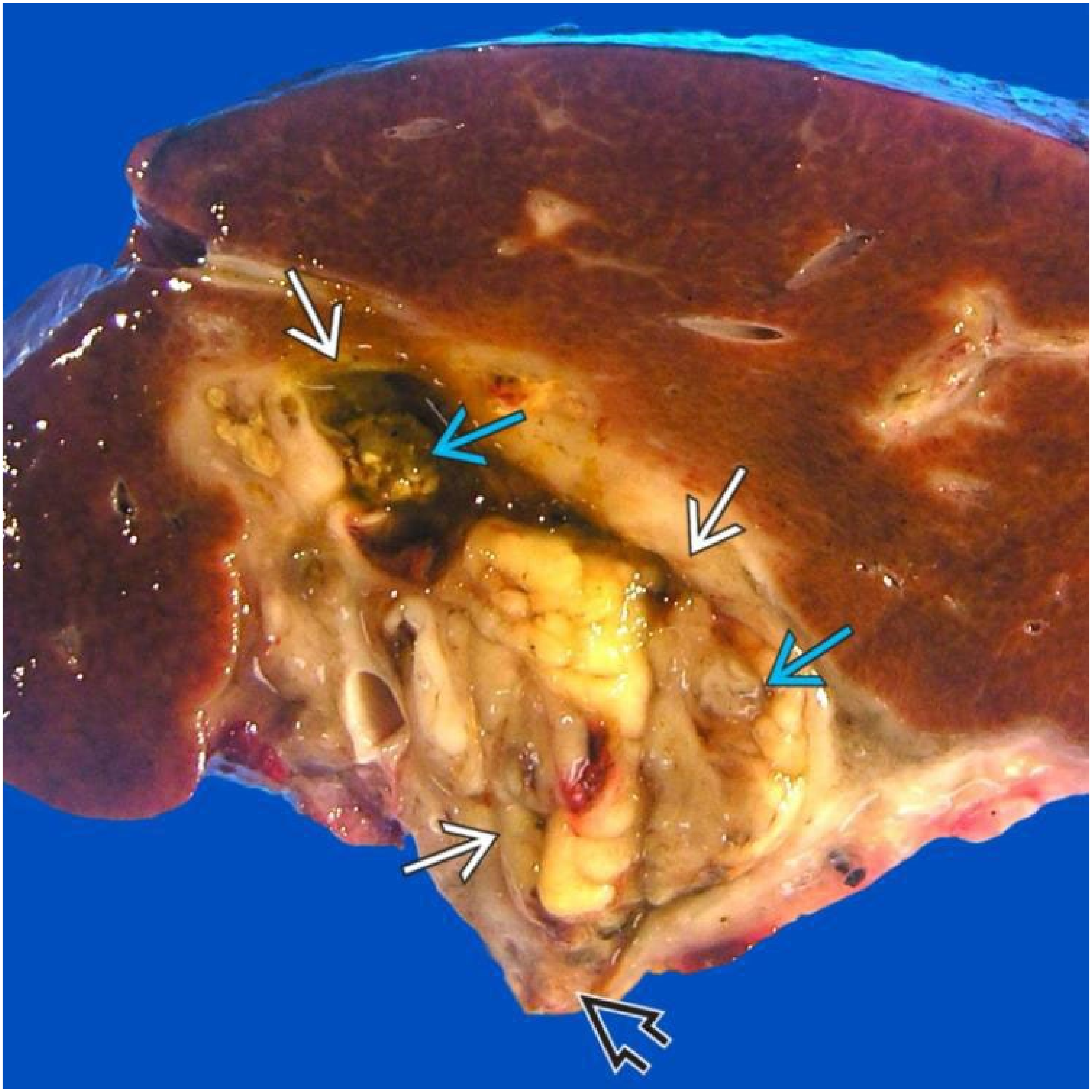
- More common in biliary tree than gallbladder
  - Common bile duct is most frequent location
  - Also reported in hepatic ducts, cystic duct, and ampulla of Vater
- Polypoid or grape-like (botryoid) gelatinous masses in lumen of bile duct or gallbladder
- May extend into liver or adhere to adjacent organs such as duodenum, stomach, and pancreas

Microscopic

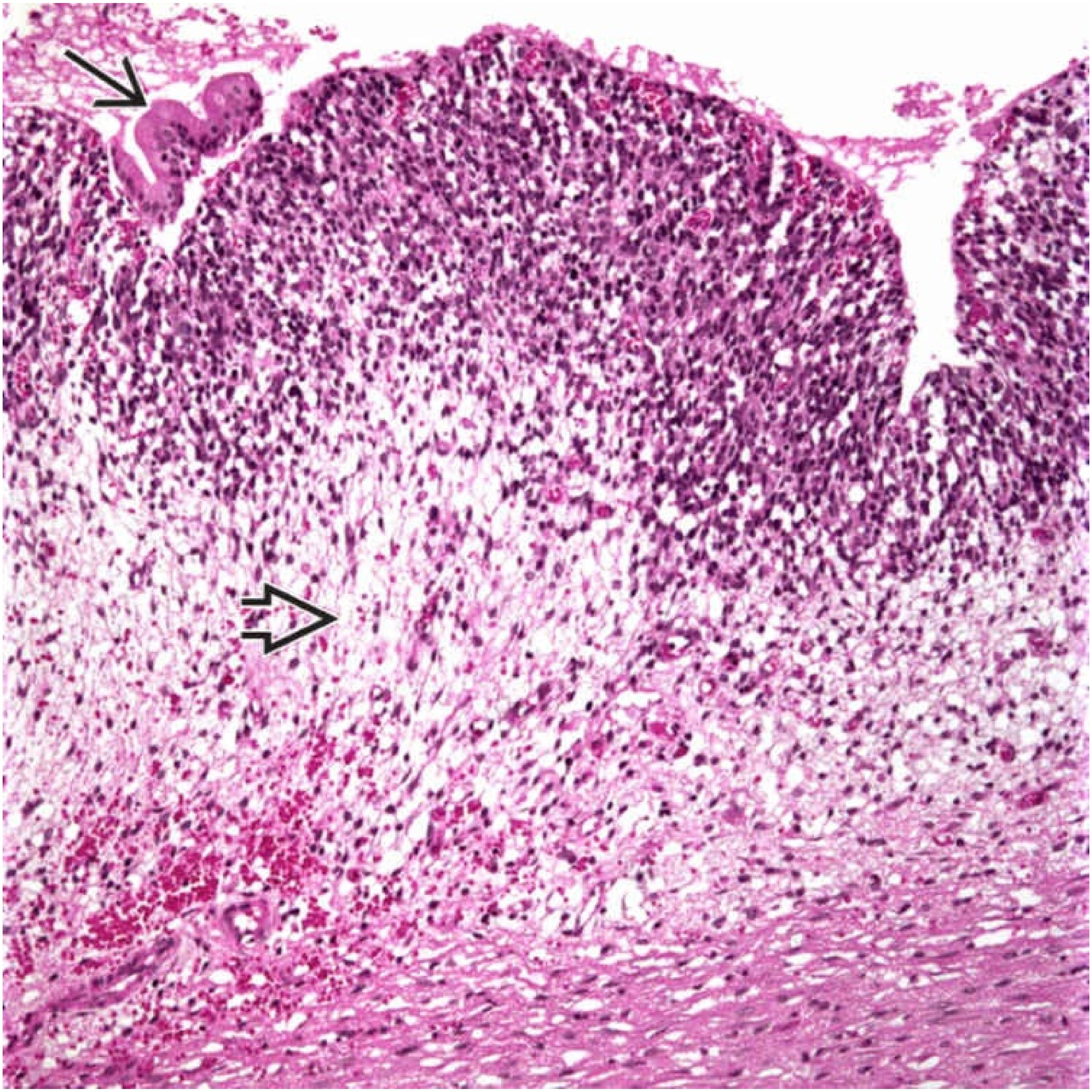
- Tumor cells densely packed beneath single layer of biliary epithelium to form characteristic “cambium layer”
  - Tumor cells typically have small round or ovoid hyperchromatic nuclei and variable amounts of eosinophilic cytoplasm
  - Spindled cells may be present and can be prominent
  - Varying numbers of rhabdomyoblasts
  - Large round or elongated cells with abundant eosinophilic granular or fibrillar cytoplasm
  - Elongated cells are referred to as strap cells
  - May show cytoplasmic cross striations

Ancillary Tests

- Myogenic differentiation shown by positive immunostains for myogenin, MYOD1, desmin, muscle specific actin

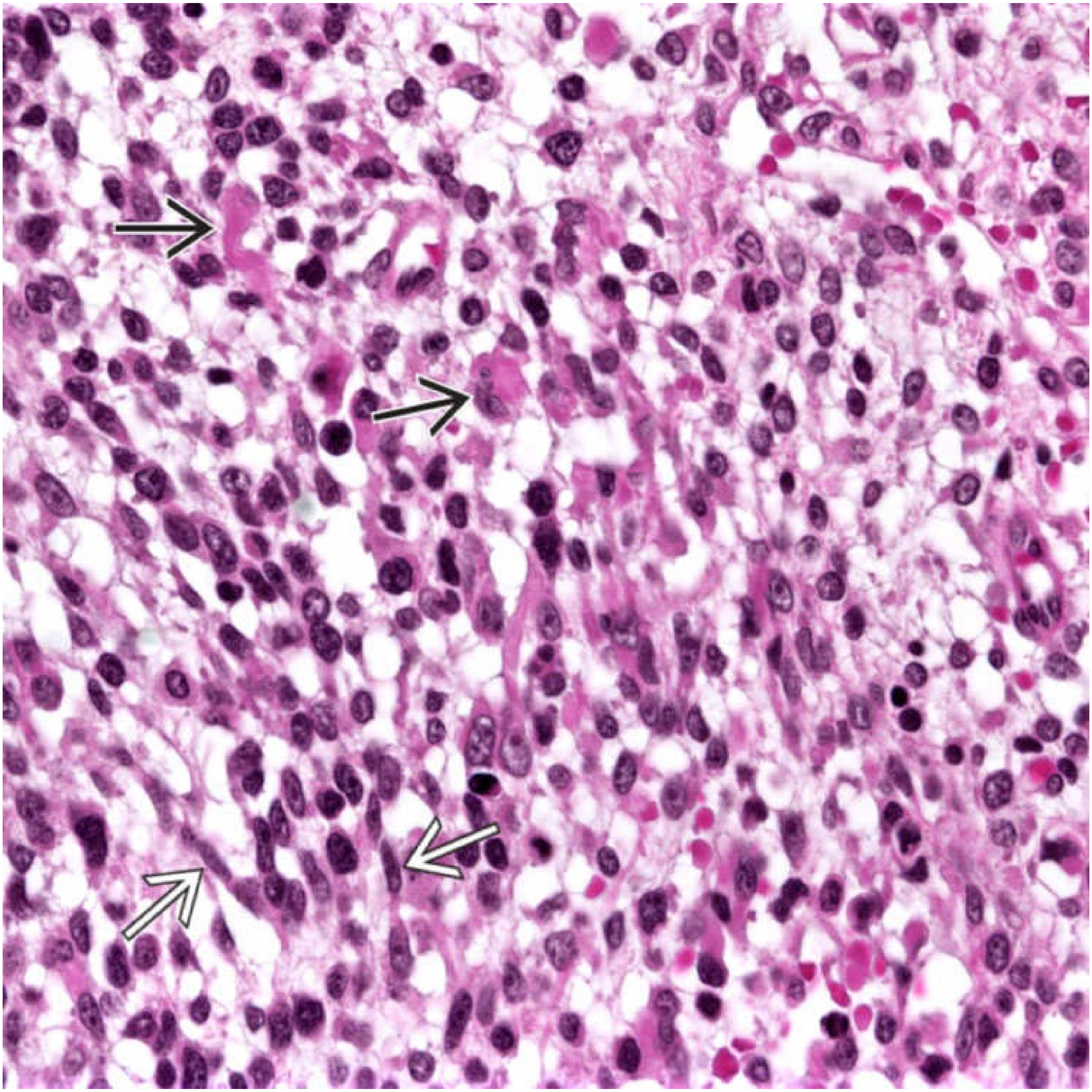


Mass in Common Hepatic Duct
Liver of a 2-year-old girl shows a large embryonal rhabdomyosarcoma (RMS) in the porta hepatis. Mass → obstructs common hepatic duct ⇒ and extends to hepatic duct resection margin ➪. It shows a variegated cut surface due to necrosis caused by neoadjuvant chemoradiation therapy.



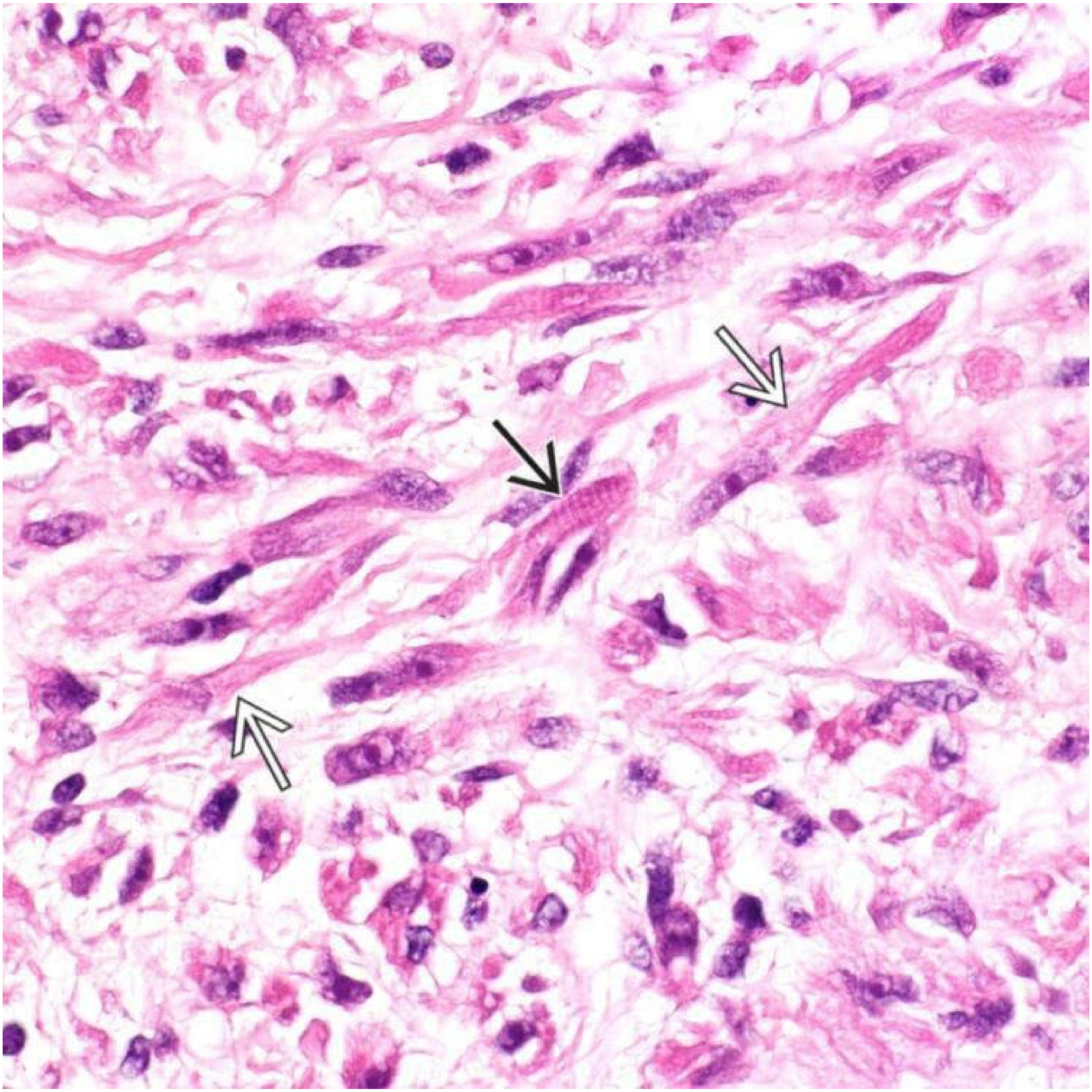
Cambium Layer

Characteristic cambium layer consists of densely packed tumor cells beneath biliary epithelium →, which is largely denuded. Deeper portion of tumor is hypocellular with loose myxoid stroma ⇨ .



Small Round Tumor Cells

Tumor cells in embryonal RMS are typically small, round or ovoid, and hyperchromatic. Spindled cells can be present ⇨. Occasional rhabdomyoblasts are seen, which have abundant eosinophilic cytoplasm → .



Strap Cells
This case of embryonal RMS shows a focal area with multiple elongated strap cells with abundant eosinophilic cytoplasm. Cytoplasmic cross striations are noted in one cell.

TERMINOLOGY

Abbreviations

- Rhabdomyosarcoma (RMS)

Definitions

- Primary RMS, embryonal type, arising in biliary tree and gallbladder

CLINICAL ISSUES

Epidemiology

- Age
  - Most frequently described in children, in extrahepatic biliary tree
    - Mean: 3-4 years (range: 16 months to 11 years)
    - 1% of all RMS occurring in children
    - Most common malignant neoplasm of extrahepatic biliary tree in children
  - Occasionally seen in adults, usually in gallbladder
- Sex
  - No predilection

Presentation

- Signs of progressive biliary obstruction
  - Jaundice, acholic stools
- Abdominal distension &/or pain
- Fever, anorexia

Treatment

- Surgery, chemotherapy, radiotherapy

Prognosis

- Generally poor
  - Metastasis occurs in 40% of cases
  - Death usually results from local complications
  - Long-term survival can be achieved with modern multimodality therapy
    - Estimated 5-year survival rate: 66%

MACROSCOPIC

General Features

- More common in biliary tree than gallbladder
  - Common bile duct is most frequent location
  - Also reported in hepatic ducts, cystic duct, and ampulla of Vater
- Polypoid or grape-like (botryoid) gelatinous masses in lumen of bile duct or gallbladder
- May extend into liver or adhere to adjacent organs such as duodenum, stomach, and pancreas
- Can be as large as 20 cm

MICROSCOPIC

Histologic Features

- Resembles botryoid-type embryonal RMS elsewhere in body
  - Single layer of biliary epithelium covering tumor
    - Epithelium may be intact, ulcerated, or inflamed
  - Tumor cells typically have small round or ovoid hyperchromatic nuclei and variable amounts of eosinophilic cytoplasm
    - Tumor cells densely packed beneath epithelium to form characteristic cambium layer
    - Usually hypocellular with loose myxoid stroma deeper in lesion
    - Spindled cells may be present and can be prominent
    - Mitotic and apoptotic counts may be very high
  - Varying numbers of rhabdomyoblasts
    - Large round or elongated cells with abundant eosinophilic granular or fibrillar cytoplasm
    - Elongated cells are referred to as strap cells
      - May show cytoplasmic cross striations
      - More common in cases with prominent spindled cell component

ANCILLARY TESTS

Immunohistochemistry

- Myogenic differentiation shown by positive stains for myogenin, MYOD1, desmin, muscle specific actin

DIFFERENTIAL DIAGNOSIS

Sarcomatoid Carcinoma

- Lacks cambium layer and rhabdomyoblasts
- Lacks myogenic differentiation by immunohistochemistry
- Positive for cytokeratins

Leiomyosarcoma

- Lacks cambium layer and rhabdomyoblasts
- Does not mark with myogenin and MYOD1

Hepatic Undifferentiated Embryonal Sarcoma

- Typically shows marked nuclear pleomorphism

- Cytoplasmic hyaline globules frequently present
- Lacks myogenin and MYOD1 positivity

Primitive Neuroectodermal Tumor

- May have pseudorosette formation
- Lacks cambium layer and rhabdomyoblasts
- CD99(+) (RMS usually negative)
- Has *EWSR-1* translocation

Angiosarcoma

- Lacks cambium layer and rhabdomyoblasts
- Marks with vascular markers

Kaposi Sarcoma

- Marks with vascular markers and HHV8
- Seen in immunocompromised persons

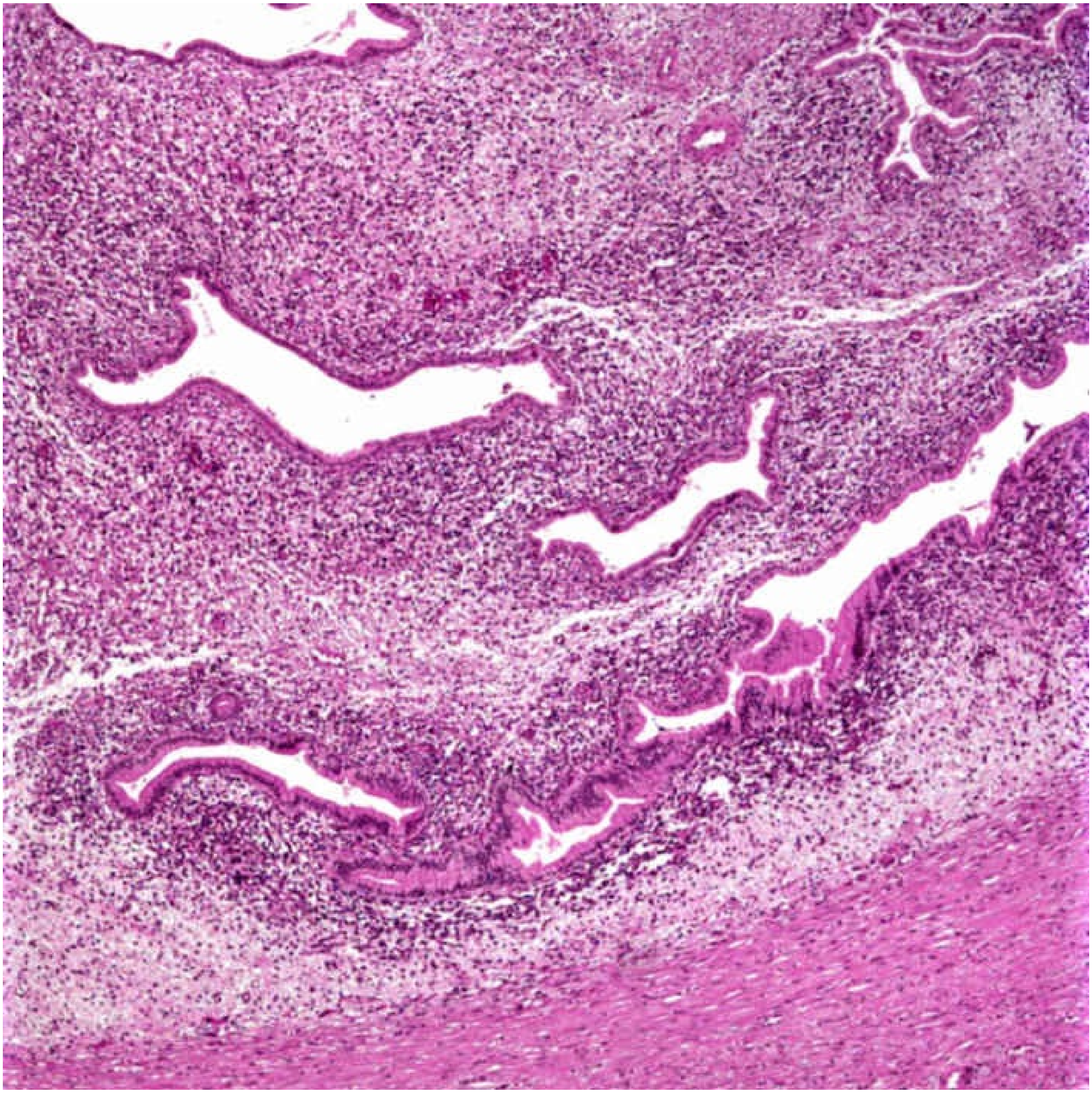
Inflammatory Pseudotumor

- Lacks cambium layer and rhabdomyoblasts
- More inflammation than RMS
- Lacks myogenin and MYOD1 positivity

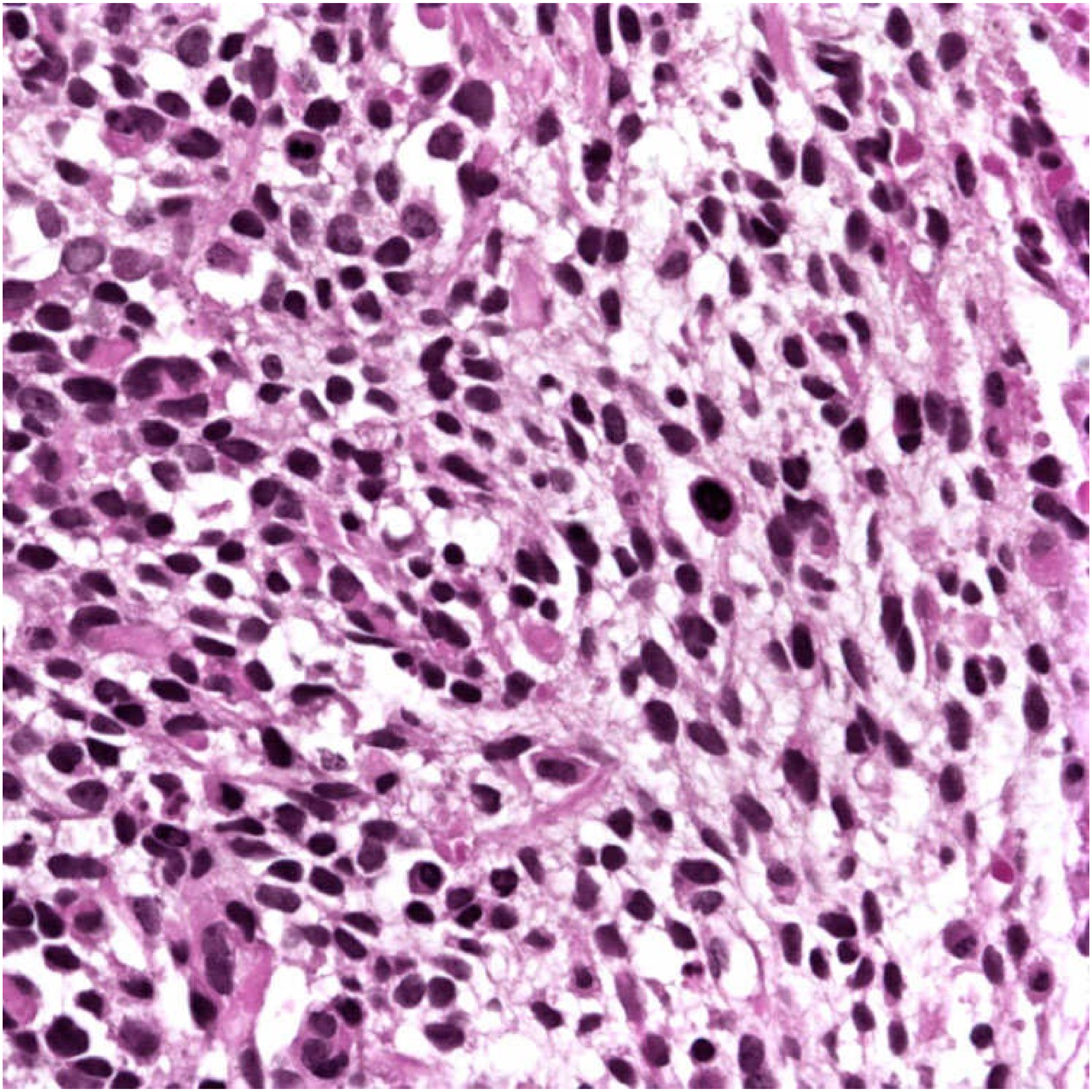
DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

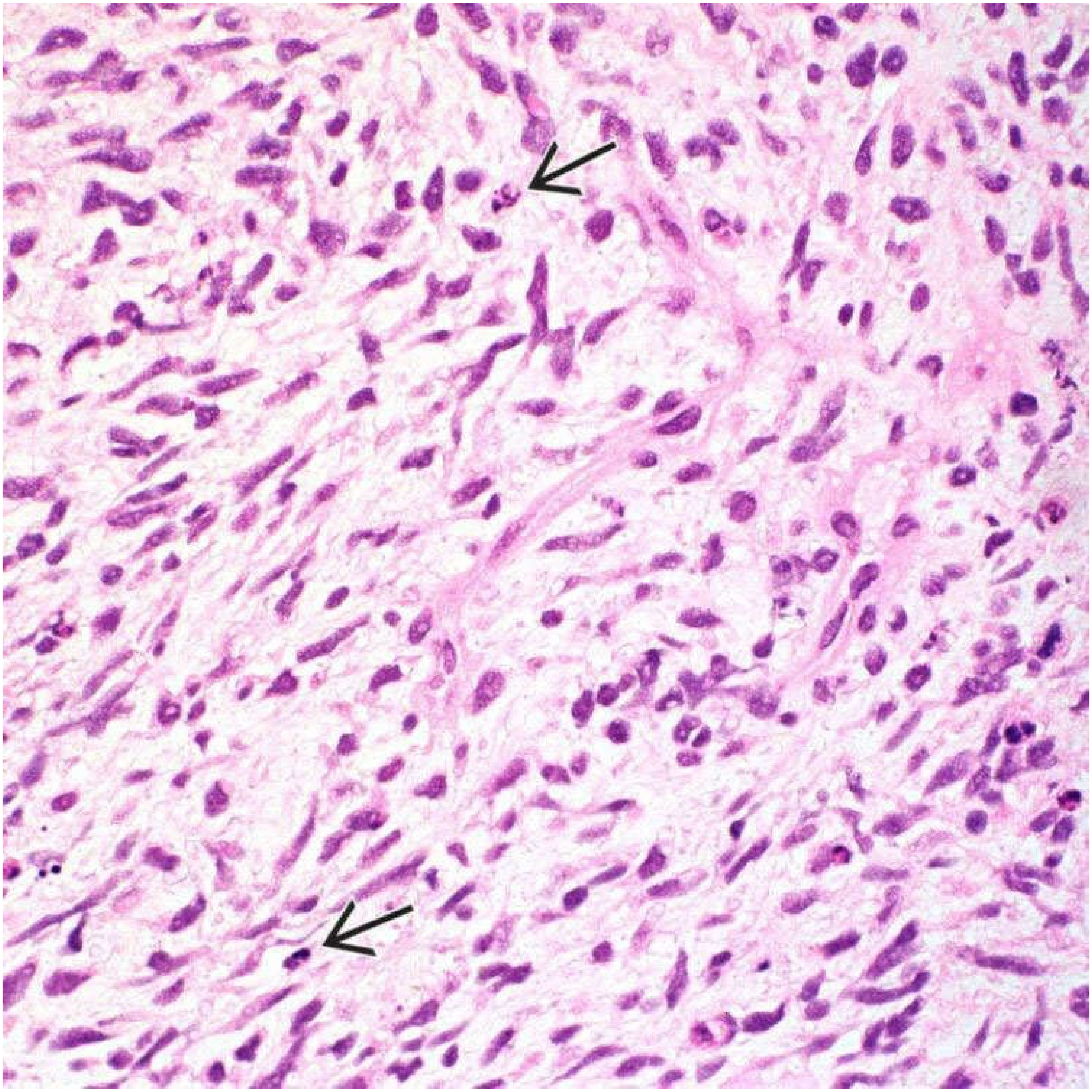
- Small hyperchromatic cells forming cambium layer beneath biliary epithelium



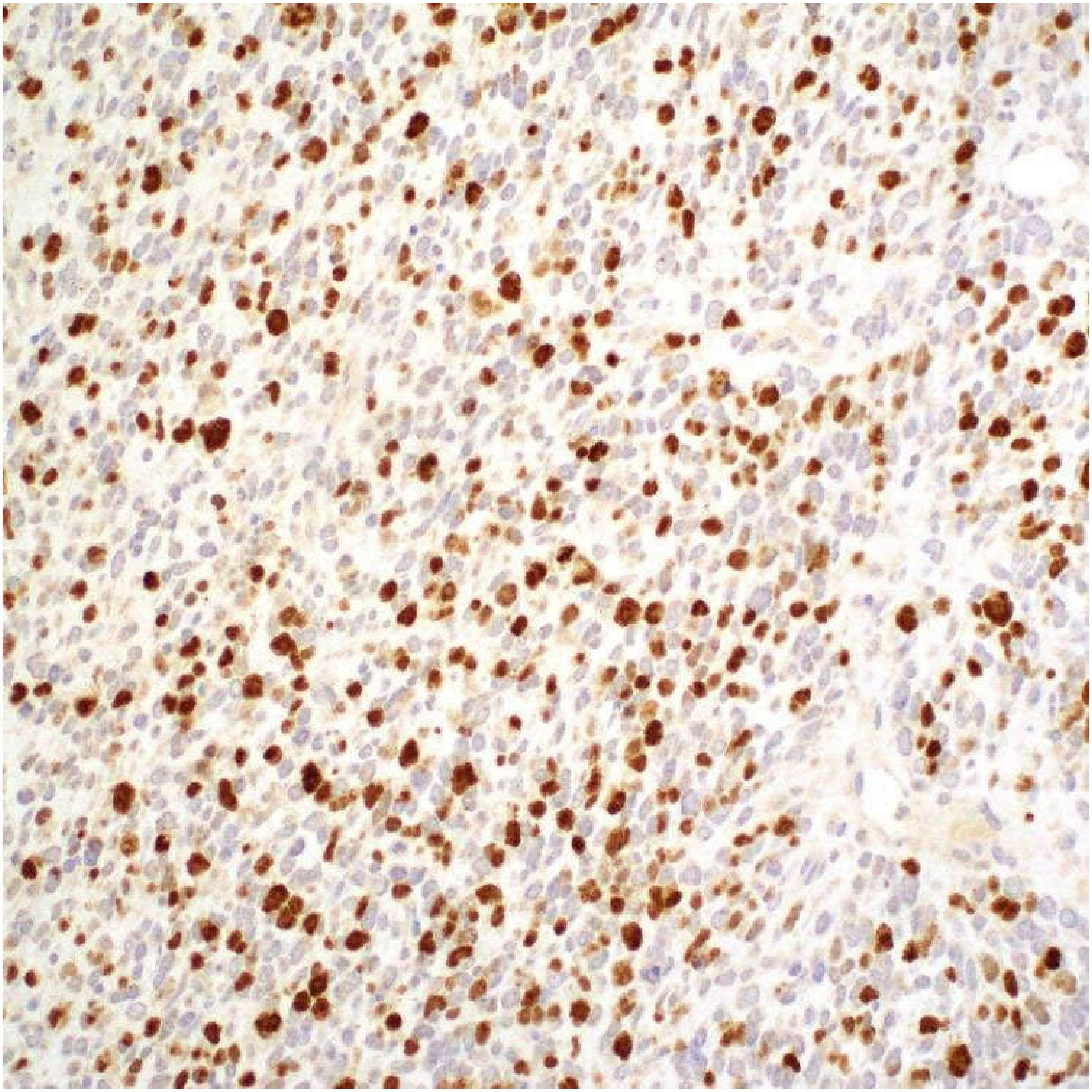
This embryonal RMS of the bile duct in a child forms a polypoid mass beneath the biliary epithelium. H&E section shows characteristic cambium layer.

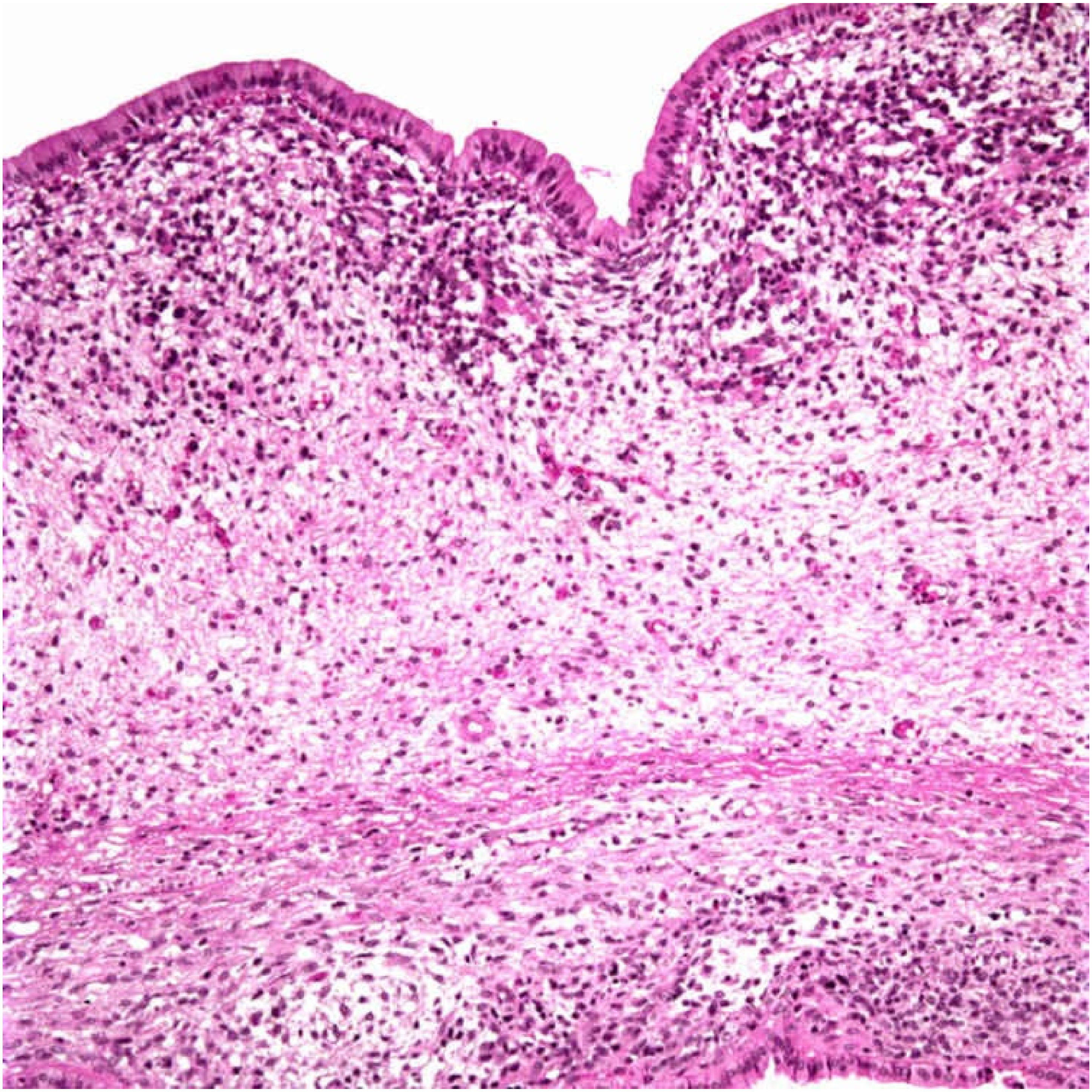


The tumor cells in embryonal RMS are typically small and hyperchromatic with a variable amount of eosinophilic cytoplasm.



Embryonal RMS of the common bile duct in a 27-month-old boy shows prominent spindled cells. Apoptotic bodies are frequent in this case →.


Tumor cells of embryonal RMS express myogenic markers such as myogenin, as demonstrated in this case.



Closely packed tumor cells of embryonal RMS form a dense cambium layer beneath a layer of intact biliary epithelium. Deep to this are spindled tumor cells within a loose myxoid stroma.

SELECTED REFERENCES

1. Paganelli, M, et al. A child with unresectable biliary rhabdomyosarcoma: 48-month disease-free survival after liver transplantation. *Pediatr Transplant*. 2014; 18(5):E146–E151.
2. Nicol, K, et al. Distinguishing undifferentiated embryonal sarcoma of the liver from biliary tract rhabdomyosarcoma: a Children's Oncology Group study. *Pediatr Dev Pathol*. 2007; 10(2):89–97.
3. Ruymann, FB, et al. Rhabdomyosarcoma of the biliary tree in childhood. A report from the Intergroup Rhabdomyosarcoma Study. *Cancer*. 1985; 56(3):575–581.

Adenomyoma

KEY FACTS

Terminology

- Acquired lesion of gallbladder consisting of invaginations of surface epithelium into thickened muscular wall
  - Common synonyms
  - Adenomyomatosis
  - Adenomyosis
  - Diverticular disease of gallbladder

Etiology/Pathogenesis

- Most cases are associated with chronic cholecystitis
- 90% of affected individuals also have cholelithiasis

Clinical Issues

- Present in ~ 1-10% of cholecystectomy specimens, depending on series
- Predominantly affects adults
- F:M = 3:1
- Often incidental finding at cholecystectomy

Macroscopic

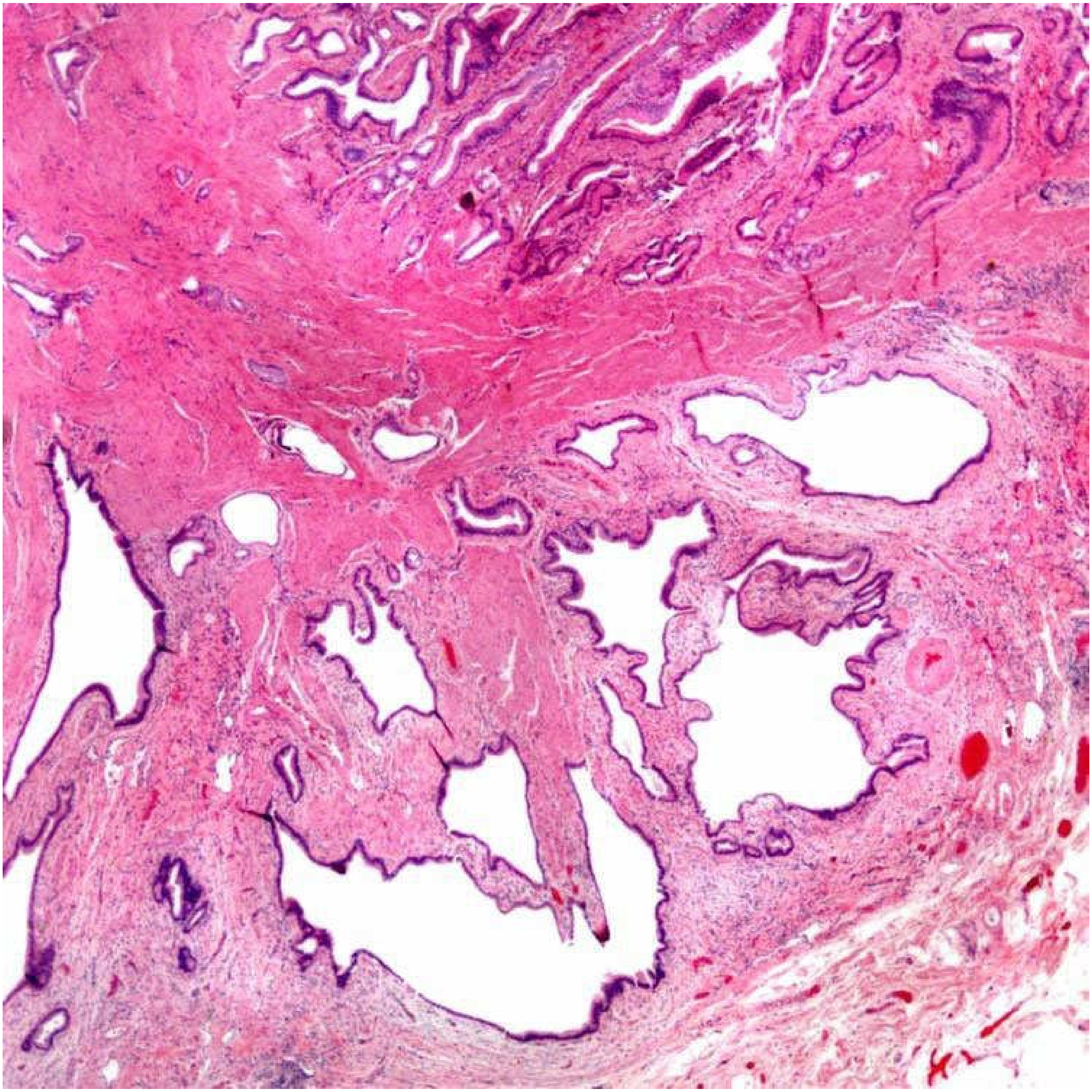
- Firm intramural area of thickening that may form polyp or mass
  - Cut surface reveals multiple cysts representing dilated biliary glands
- 3 types
  - Diffuse
  - Segmental
  - Localized

Microscopic

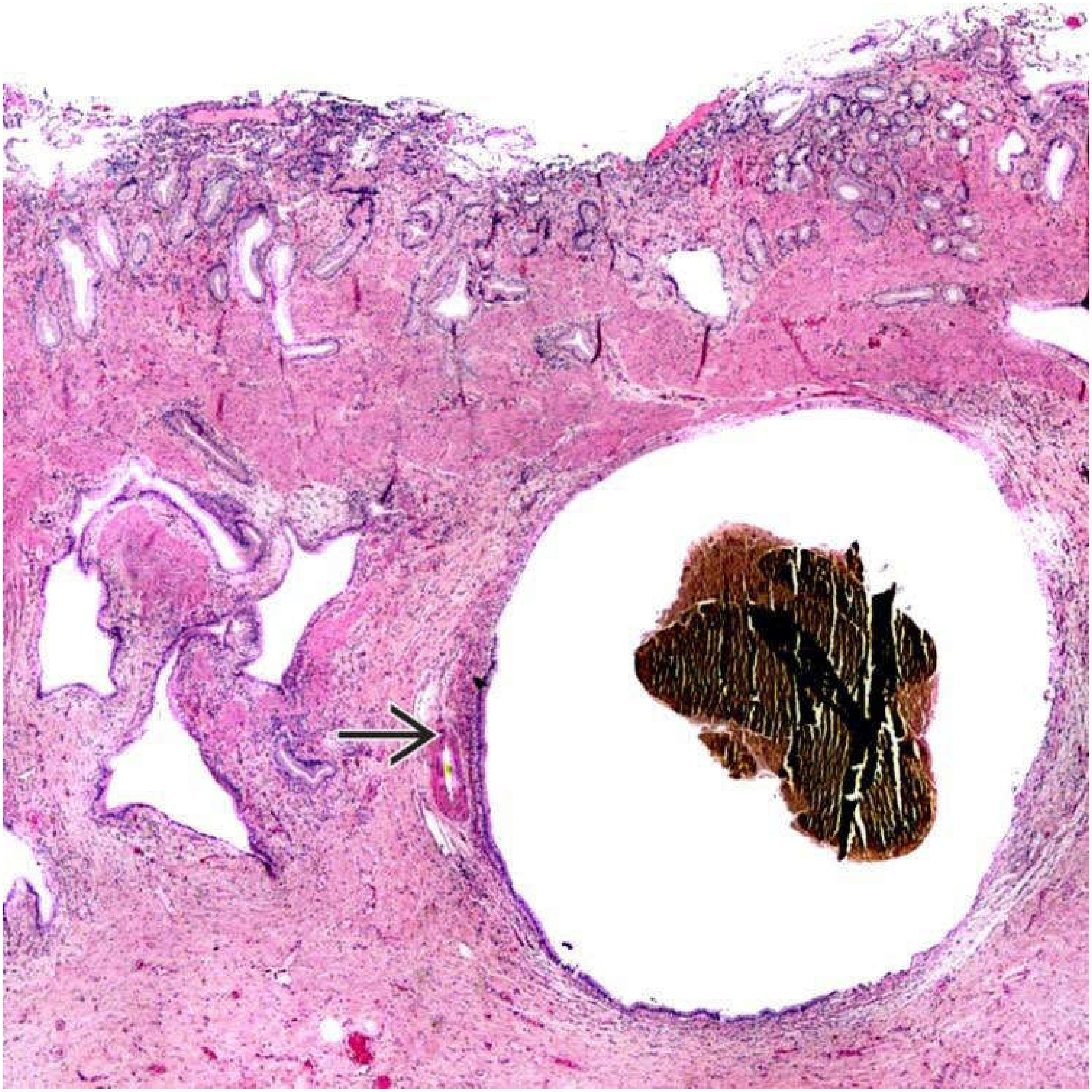
• Hypertrophic or cystically dilated glands set in hyperplastic smooth muscle
• Epithelium usually identical to that seen in normal biliary mucosa

Top Differential Diagnoses

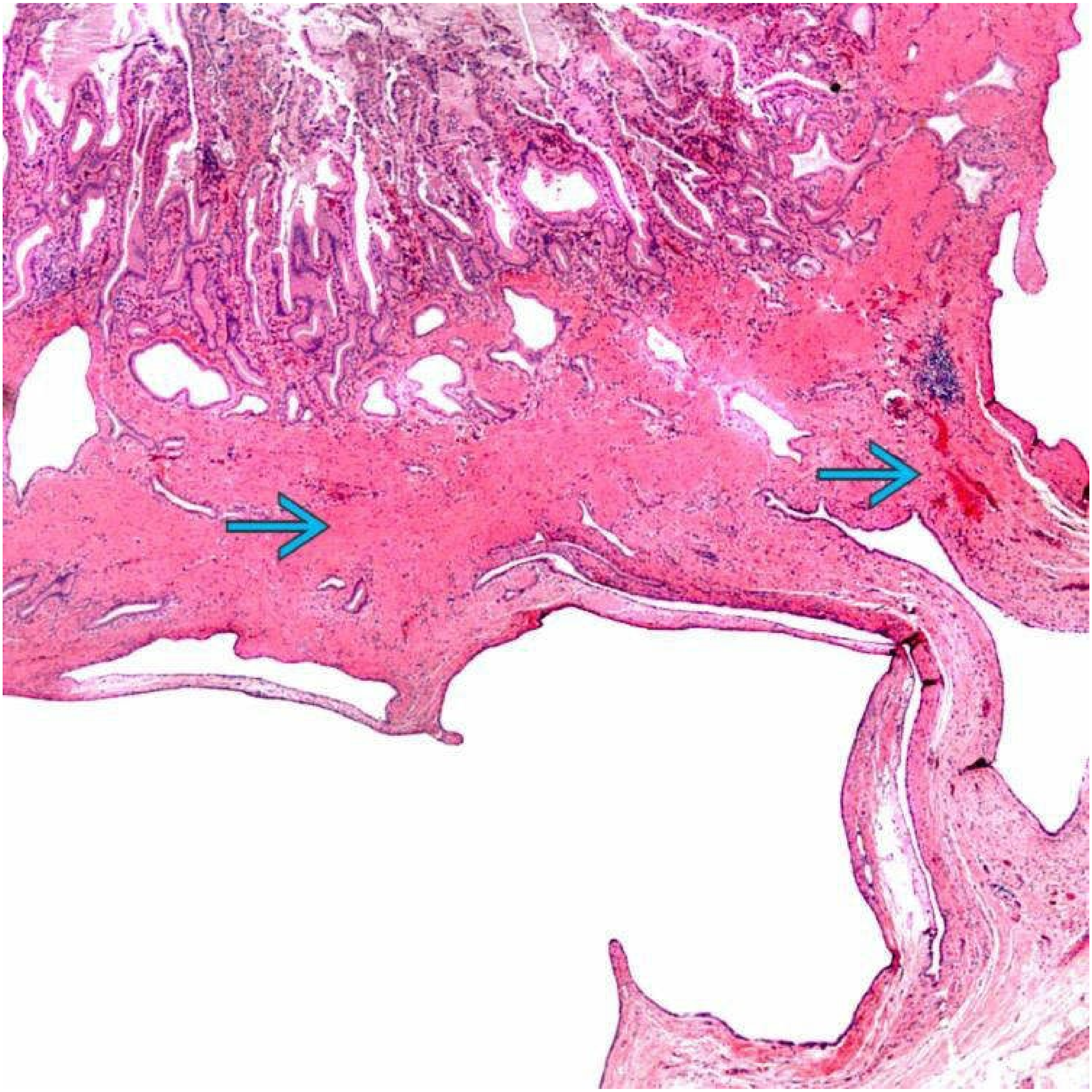
• Adenocarcinoma
• Chronic cholecystitis



Low-Power View
Low-power view of an adenomyoma in the fundus of the gallbladder shows irregular invaginations of biliary glands extending down from the surface of the gallbladder into the muscular wall.

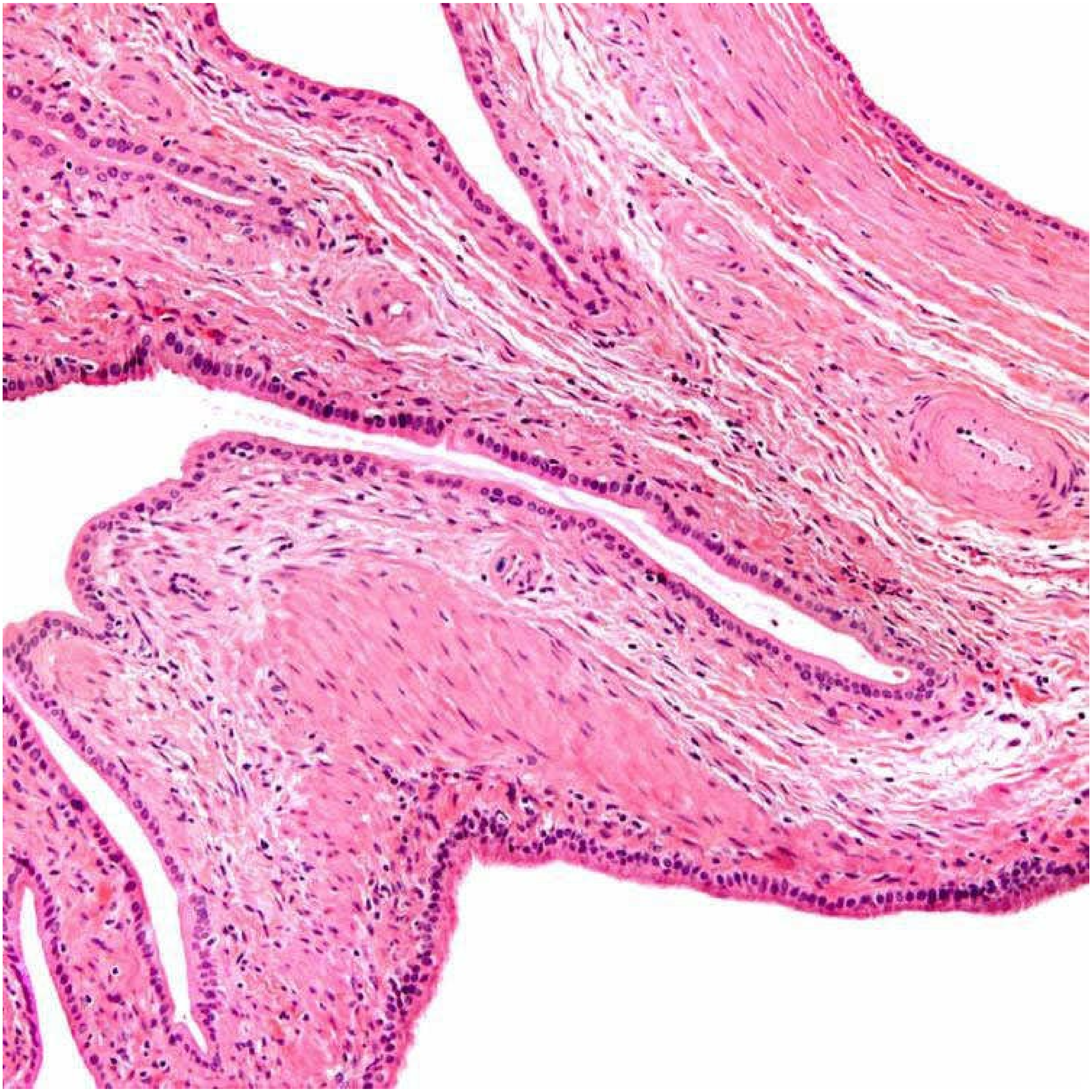


Diffuse Adenomyomatosis
This gallbladder had diffuse adenomyomatosis along the entire length of the wall. Some of the dilated glands contain inspissated bile →.



Thickened Wall

The markedly dilated glands in this adenomyoma are invested with hypertrophic smooth muscle →. Both of these features lead to thickening of the gallbladder wall.



Epithelium Lining Glands
The epithelium lining the glands is benign biliary epithelium without nuclear enlargement, nuclear pleomorphism, or mitoses. Note the hypertrophic smooth muscle in the wall.

TERMINOLOGY

Synonyms

- Adenomyomatous polyp
- Adenomyosis
- Adenomyomatous hyperplasia
- Adenomyomatosis
- Diverticular disease of gallbladder

- Intramural diverticulosis
- Cholecystitis cystica
- Cholecystitis glandularis proliferans

Definitions

- Acquired lesion of gallbladder characterized by proliferation of surface epithelium with invaginations into thickened muscularis

ETIOLOGY/PATHOGENESIS

Acquired Lesion

- Most cases are associated with chronic cholecystitis
- 90% of affected individuals also have cholelithiasis

CLINICAL ISSUES

Epidemiology

- Incidence
  - Present in ~ 1-10% of cholecystectomy specimens, depending on series
  - Represents 15-25% of benign gallbladder polyps
  - ~ 4,500 cases diagnosed in USA each year
- Age
  - Predominantly affects adults, although also reported in children
- Sex
  - F:M = 3:1

Site

- Most often occurs in fundus, within muscular wall

Presentation

- Usually asymptomatic
  - Often incidental finding at cholecystectomy
  - Associated with cholecystitis

Natural History

- Benign

Treatment

- Cholecystectomy is curative

IMAGING

Radiographic Findings

• Diffuse or focal gallbladder wall thickening seen on ultrasound, abdominal CT, or MRCP
• Accurate diagnosis relies on identification of diverticula or cystic spaces within lesion

MACROSCOPIC

General Features

• Firm intramural area of thickening
  ○ Diffuse type: Entire wall is involved from cystic duct to funds
  ○ Segmental type: Involves circumferential band or segment
  ○ Localized type: Solitary lesion at fundus
• Cut surface reveals trabecular appearance due to multiple cysts representing dilated glands
  ○ Cysts often contain inspissated bile and bile concretions
• May form polypoid or mass lesion
  ○ Those that form mass lesions may be mistaken for neoplasm

Size

• Localized type measure 0.5-2.5 cm (average size: 1.5 cm)

MICROSCOPIC

Histologic Features

• Branching &/or cystically dilated glands glands invaginating into muscular wall
  ○ Represent extensions of Rokitansky-Aschoff sinuses, which are invaginations or diverticula of biliary epithelium
  ○ Epithelium usually identical to that seen in normal biliary mucosa
  – May show reactive and metaplastic changes (usually pyloric or intestinal metaplasia)
○ Rarely, glands are seen in close proximity to nerves and should not be interpreted as perineural invasion
• Hypertrophy of muscularis is invariably present

DIFFERENTIAL DIAGNOSIS

Adenocarcinoma

• Epithelial elements penetrating smooth muscle may be confused with adenocarcinoma
• Cytologic features of malignancy are entirely lacking in adenomyoma

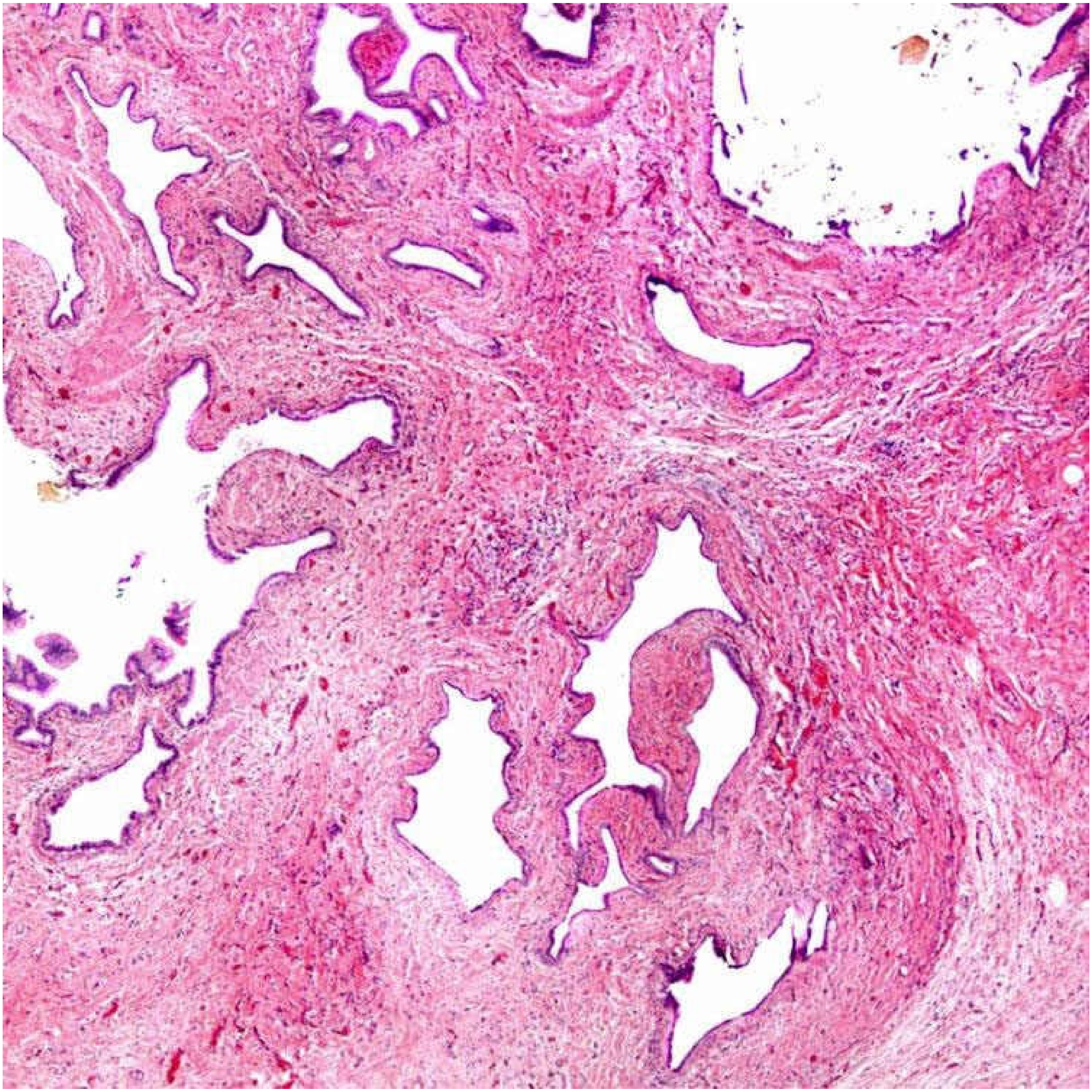
Chronic Cholecystitis

- Mild chronic inflammation with Rokitansky-Aschoff sinuses and smooth muscle hypertrophy
- Chronic cholecystitis shows less prominent glandular dilatation and muscular hypertrophy than adenomyoma
- Most patients with adenomyoma also have chronic cholecystitis

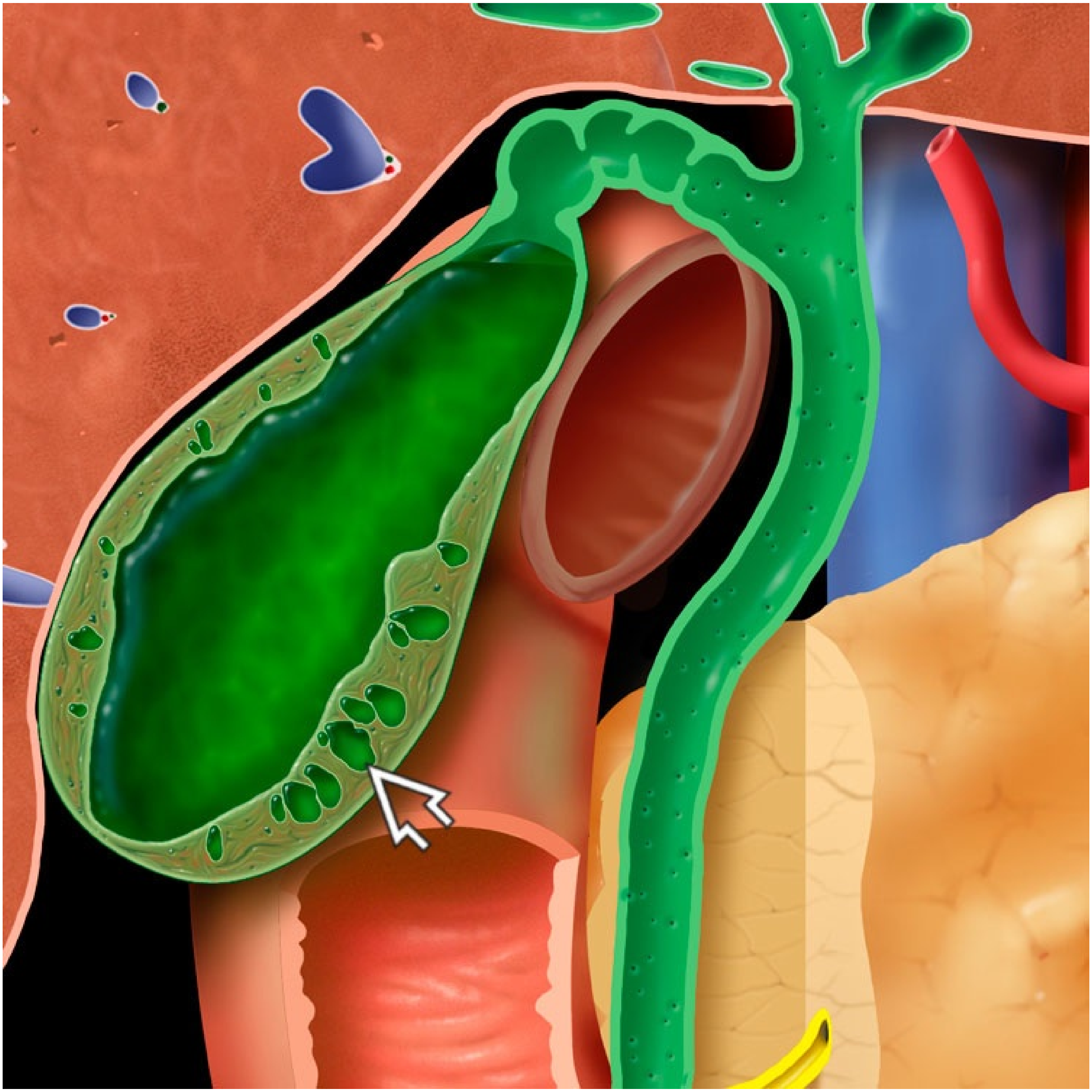
DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

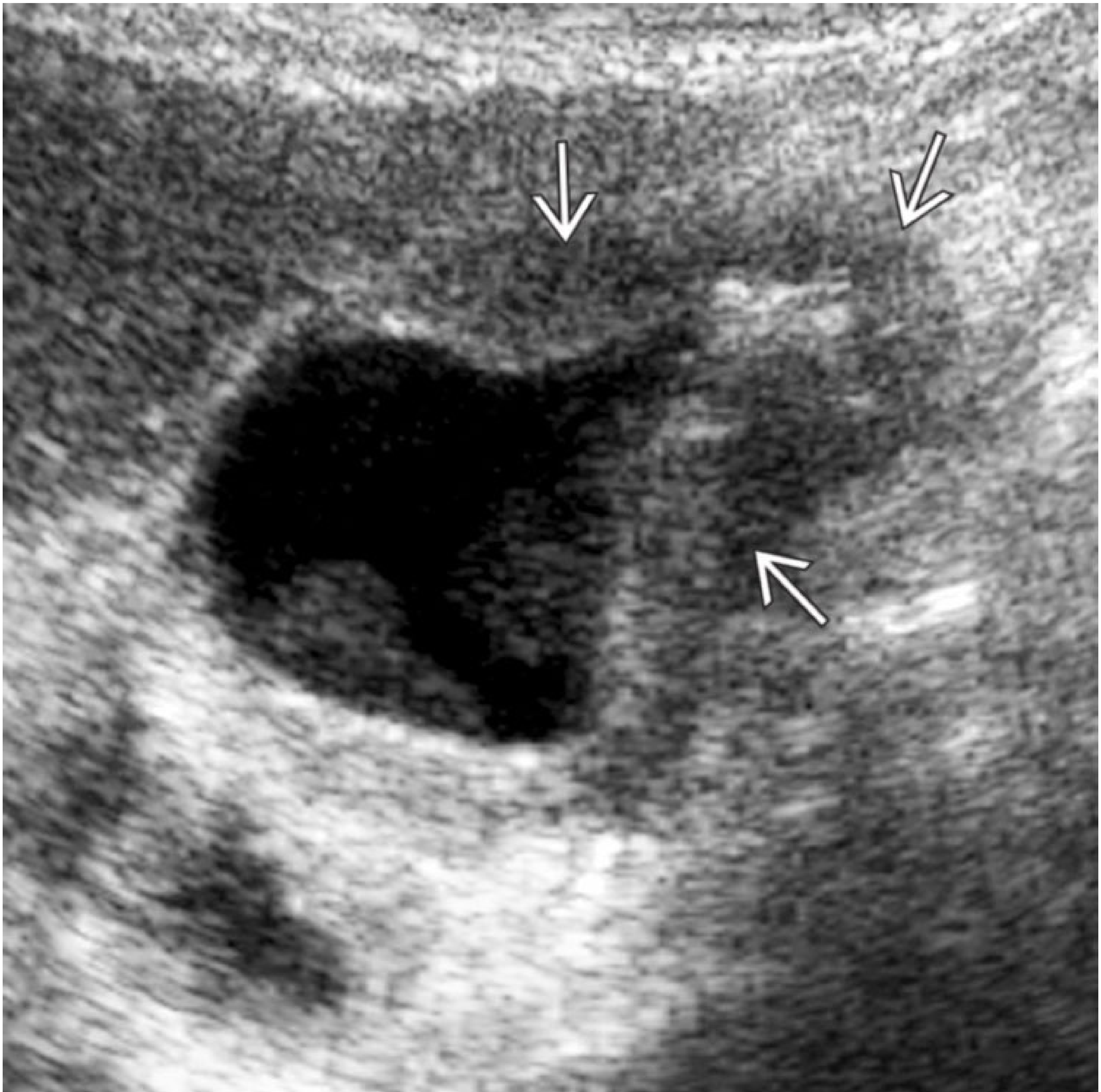
- Bland-appearing epithelium and cystically dilated glands set in thickened smooth muscle
- Associated with chronic cholecystitis and cholelithiasis



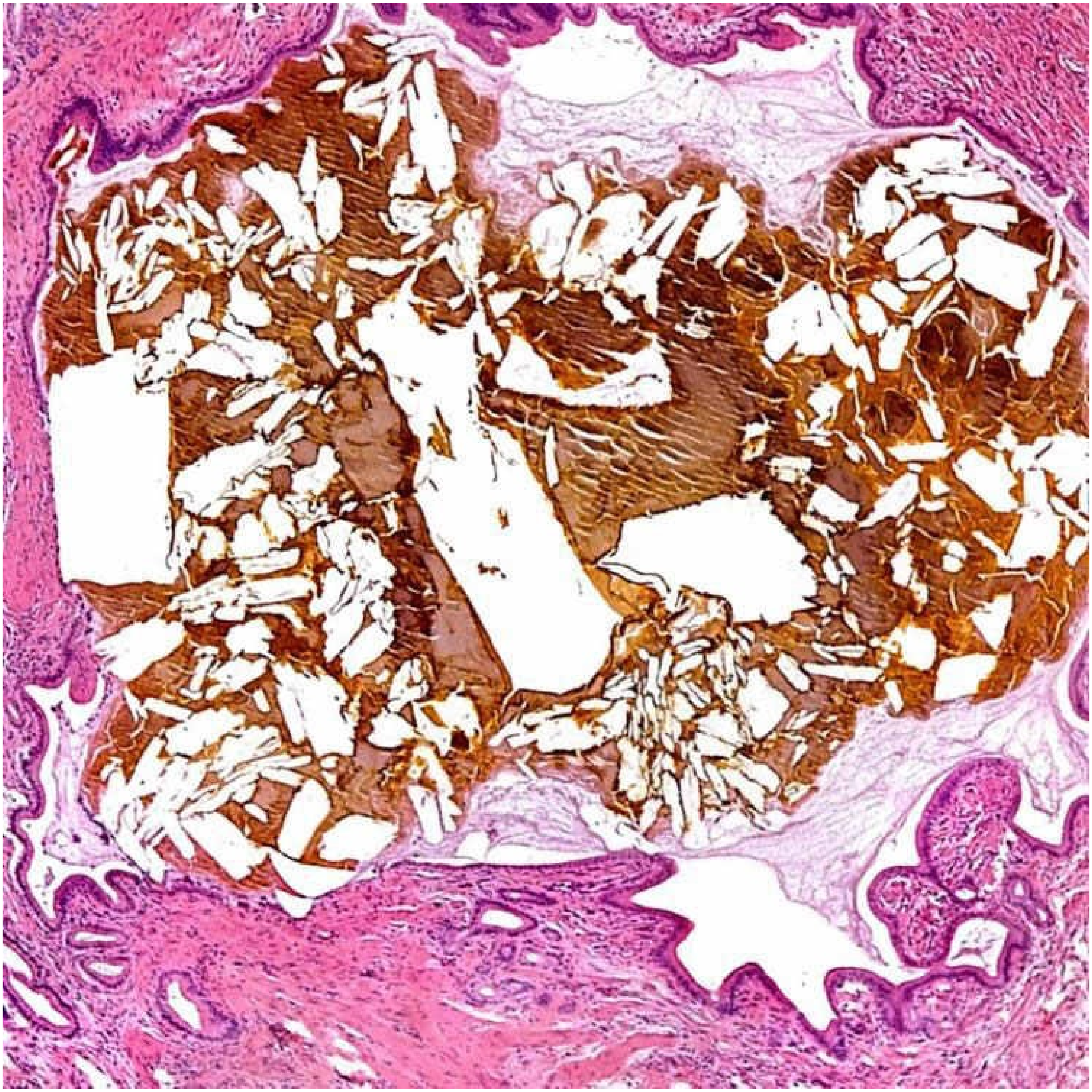
The gallbladder wall is thickened in adenomyomas. The lesion consists of irregular branching biliary glands within hypertrophic smooth muscle.



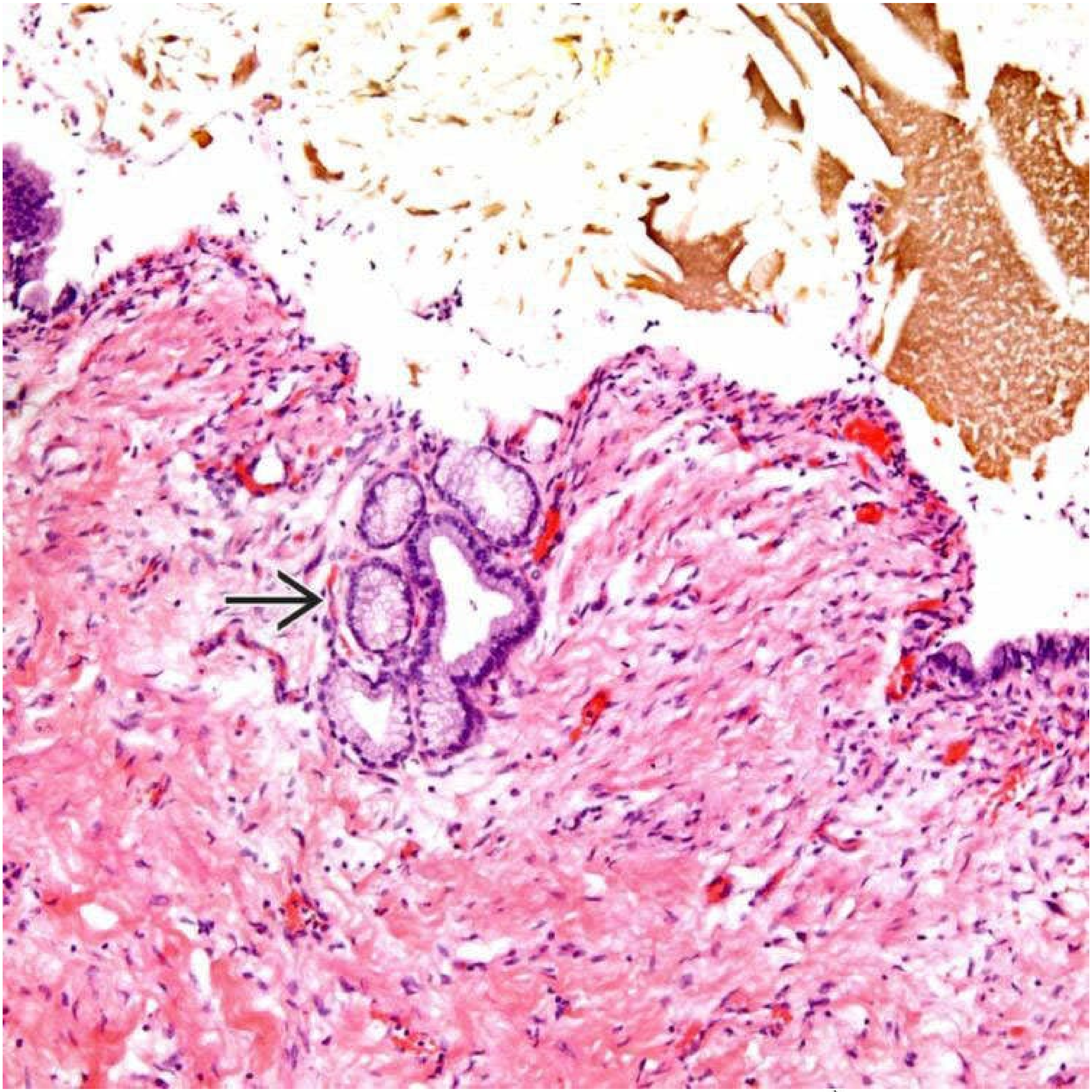
Graphic shows characteristic features of adenomyomatosis. Note the thickened gallbladder wall with multiple intramural cystic spaces ➡ .



Ultrasound of the gallbladder shows focal mural thickening in the fundus ⇒ with no invasion of adjacent structures. This is the typical appearance of adenomyomatosis.



This markedly dilated, irregular gland contains dense, inspissated bile.



Pyloric metaplasia can be seen in the glands of adenomyomas →.

SELECTED REFERENCES

1.Hayes, BD, et al. Seek and ye shall find: the importance of careful macroscopic examination and thorough sampling in 2522 cholecystectomy specimens. *Ann Diagn Pathol*. 2014; 18(3):181–186.

2.Albores-Saavedra, J, et al. Adenomyomatous hyperplasia of the gallbladder with perineural invasion: revisited. *Am J Surg Pathol*. 2007; 31(10):1598–1604.

3.Ching, BH, et al. CT differentiation of adenomyomatosis and gallbladder cancer. *AJR Am J Roentgenol*. 2007; 189(1):62–66.

4.Owen, CC, et al. Gallbladder polyps, cholesterolosis, adenomyomatosis, and acute acalculous

cholecystitis. *Semin Gastrointest Dis*. 2003; 14(4):178–188.

Inflammatory Polyps

KEY FACTS

Terminology

- Inflammatory/reactive mucosal projections virtually always associated with chronic cholecystitis or other inflammatory process
  - Historically, these lesions have poorly defined histologic criteria and have been referred to by variety of names (e.g., fibroinflammatory polyp, fibroepithelial polyp, mucosal hyperplasia)

Etiology/Pathogenesis

- Probable result of mucosal injury

Clinical Issues

- Usually asymptomatic
  - Often incidental finding at time of cholecystectomy
- Represent 15% of all benign gallbladder polyps
- Benign lesions with no malignant potential

Imaging

- May be difficult to distinguish from gallstones or malignancy

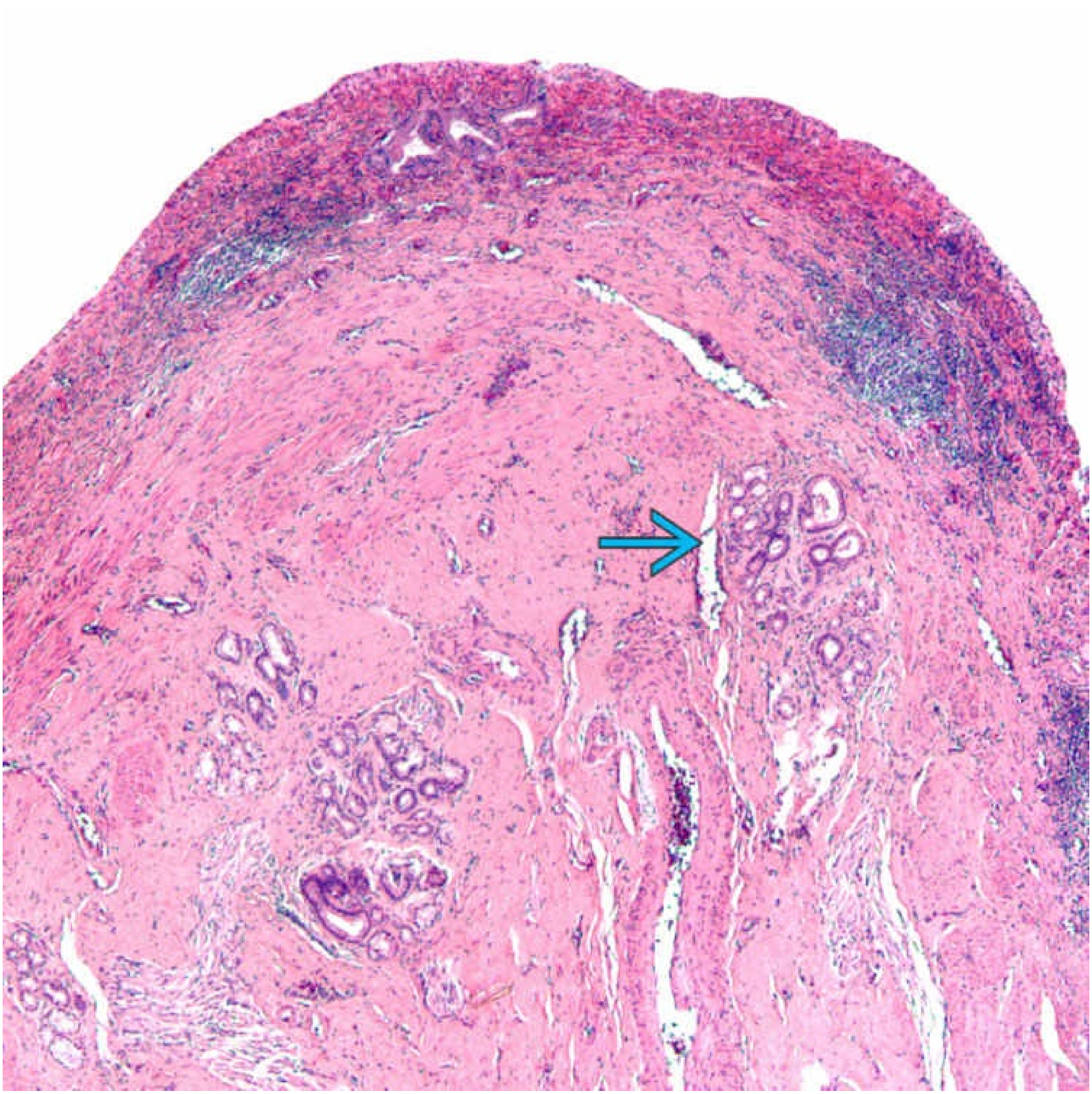
Macroscopic

- Usually solitary, sessile, red-gray or brown mucosal projections
- Typically range from 3-15 mm

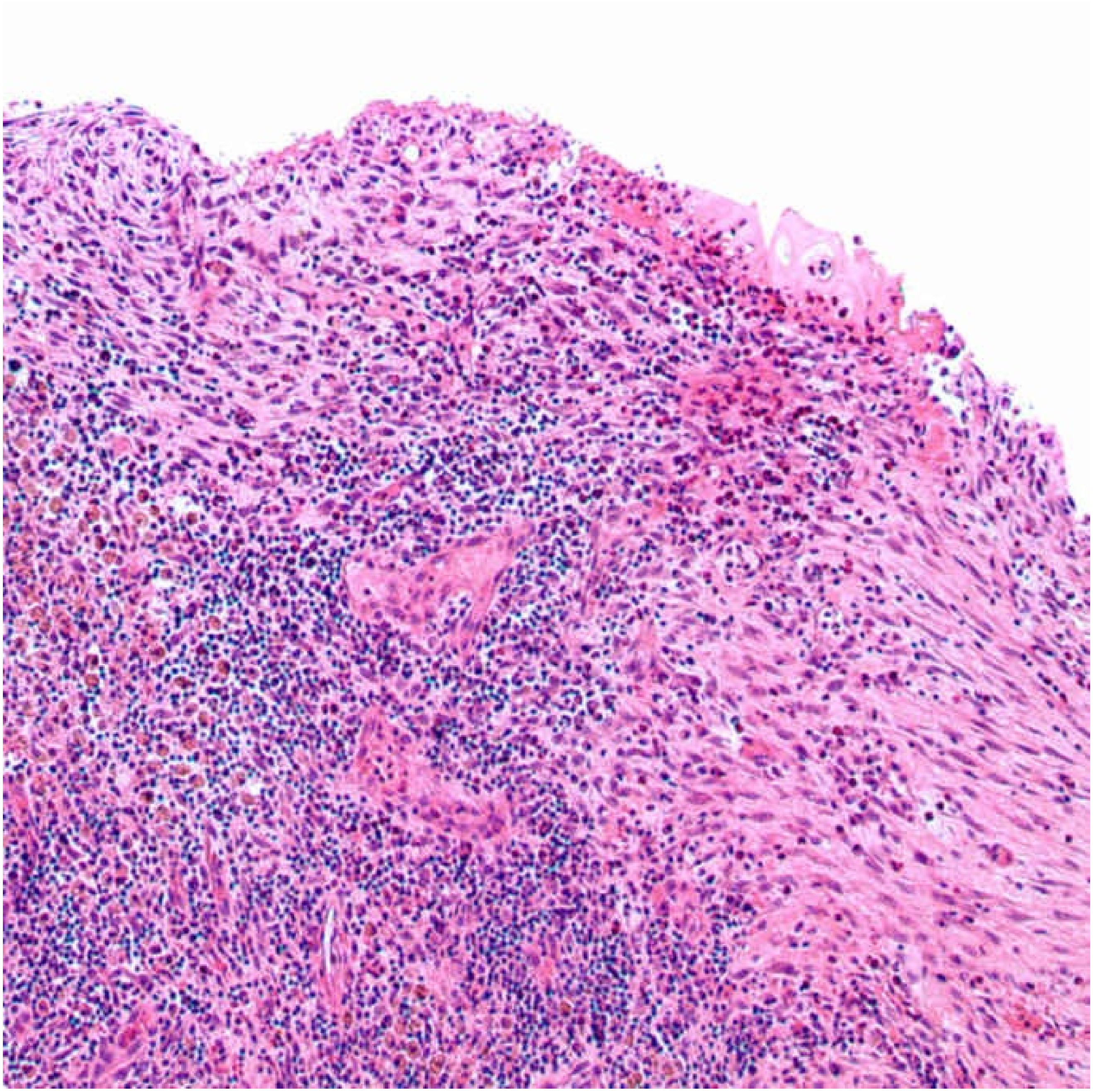
Microscopic

- Inflamed, edematous stroma
  - Acute and chronic inflammation and granulation tissue

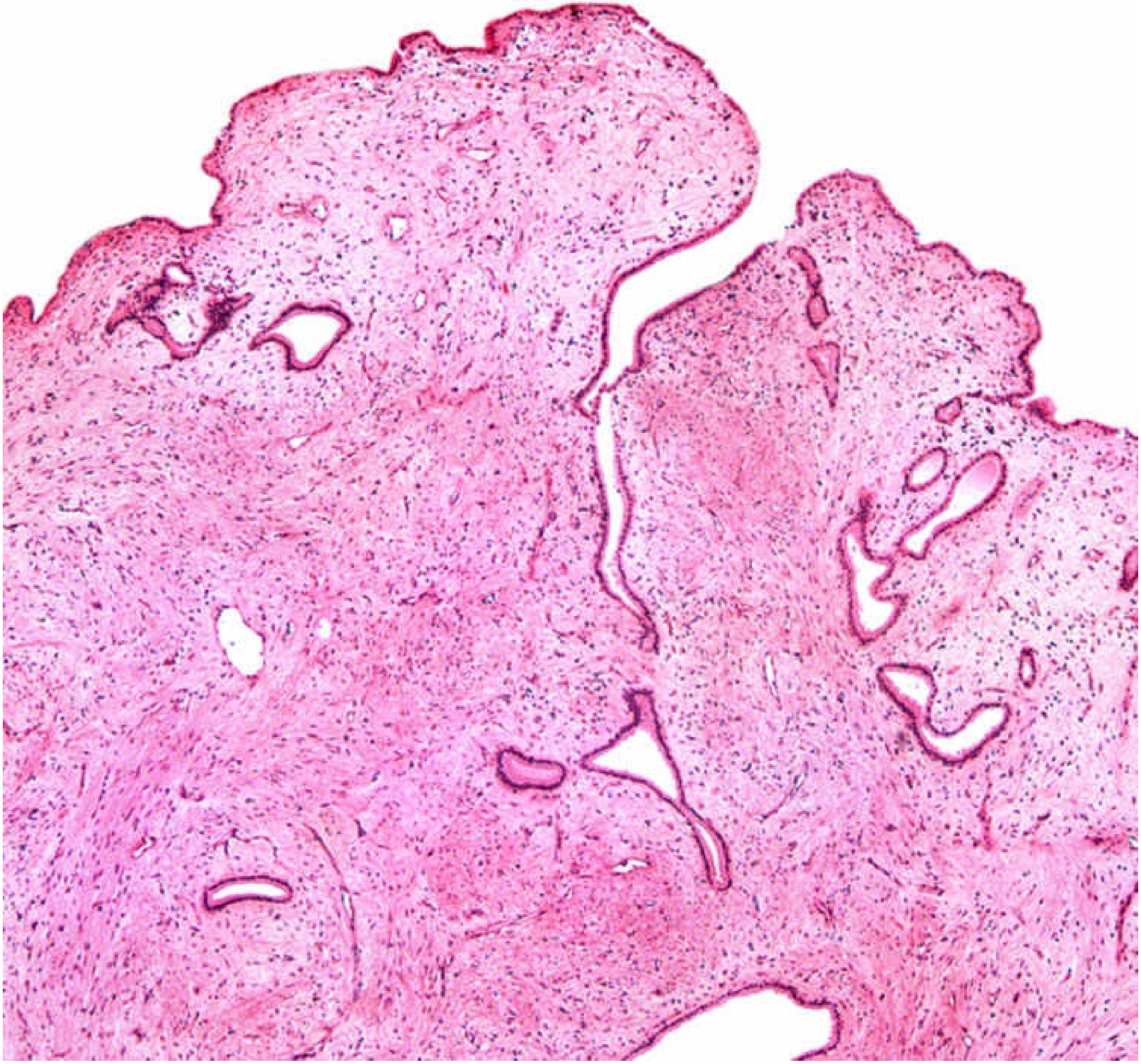
- Epithelium may show reactive changes or be denuded
- Clusters of pyloric-type glands may be present
  - Should not be misinterpreted as evidence of pyloric-type intracholecystic papillary/tubular neoplasm



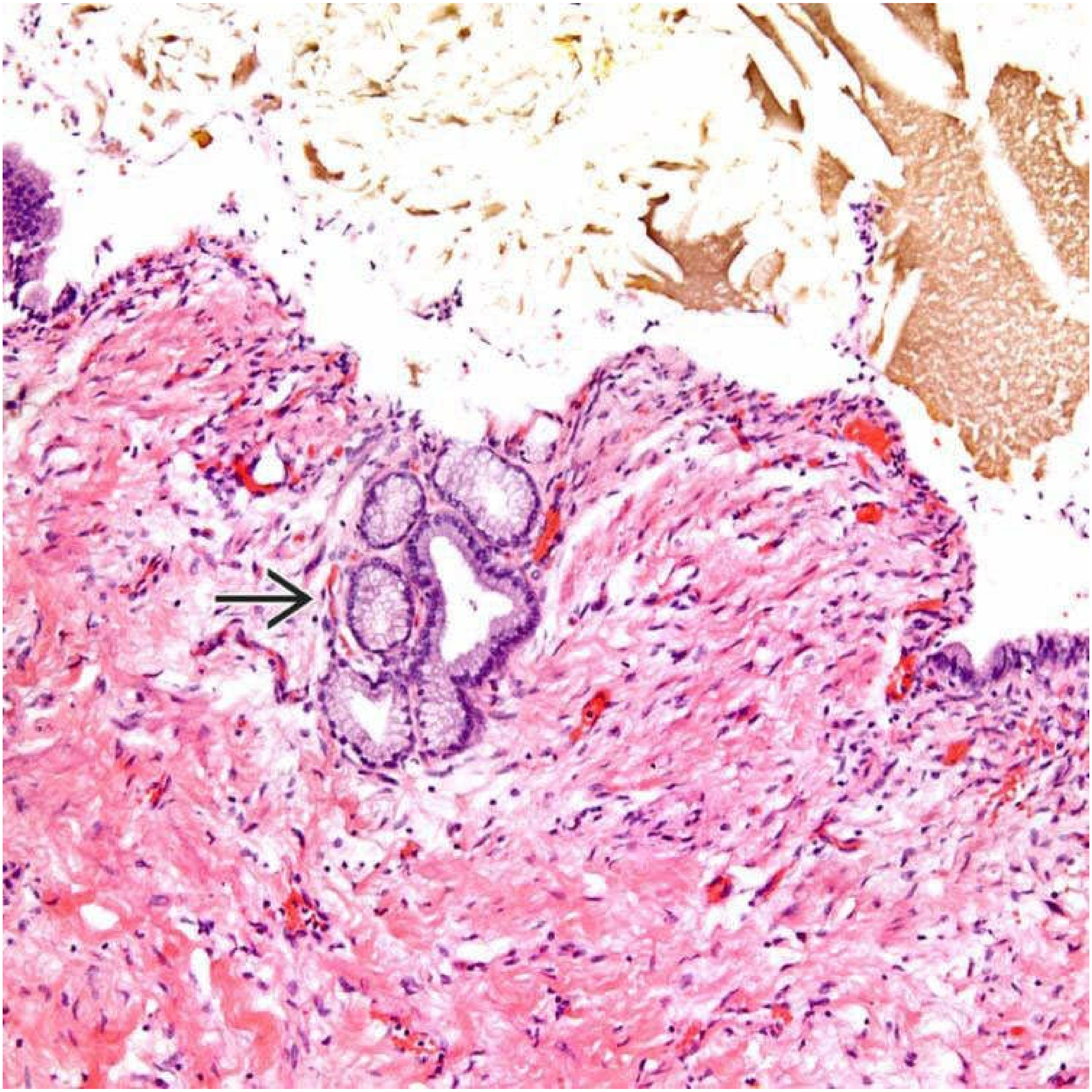
Ulceration and Granulation Tissue
An inflammatory polyp of the gallbladder shows mucosal ulceration and granulation tissue, as well as stromal inflammation and foci of mucosa with pyloric-type metaplasia → .



Inflammation and Granulation Tissue
Inflammatory polyps of the gallbladder are usually secondary to inflammatory processes and thus are composed of inflammation and a proliferation of organizing granulation tissue.



Stromal Edema
This inflammatory/reactive mucosal polyp shows stromal edema with overlying benign gallbladder epithelium.



Pyloric Metaplasia
Many inflammatory/reactive gallbladder polyps contain foci of pyloric metaplasia →, which should not be misinterpreted as evidence of a pyloric-type intracholecystic papillary/tubular neoplasm. Note the surrounding inflammation and stromal edema.

TERMINOLOGY

Synonyms

- Fibroinflammatory polyp
- Fibroepithelial polyp
- Granulation tissue polyp
- Mucosal hyperplasia

Definitions

- Inflammatory mucosal lesion associated with underlying inflammatory process
  - Poorly defined histologic criteria
  - Terms often used interchangeably

ETIOLOGY/PATHOGENESIS

Mucosal Inflammation

- Associated with chronic cholecystitis or some other inflammatory insult
- Likely develop as result of mucosal injury

CLINICAL ISSUES

Epidemiology

- Incidence
  - Represent 15% of all benign gallbladder polyps
- Sex
  - Affects females and males

Presentation

- Usually asymptomatic and found incidentally at time of cholecystectomy

Treatment

- Surgical approaches
  - Cholecystectomy recommended for symptomatic or large (> 10 mm) lesions identified on imaging
    – For larger polyps, surgery is performed to exclude possibility of malignancy
  - Cholecystectomy is curative

Prognosis

- Benign inflammatory lesions with no malignant potential

IMAGING

General Features

- Polypoid lesion may be seen on ultrasound or CT scan
- May be difficult to distinguish from gallstones or malignancy

MACROSCOPIC

General Features

- Red-gray or brown mucosal projections
- Usually sessile
- Often solitary

Size

- Typically range from 3-15 mm

MICROSCOPIC

Histologic Features

- Ulcerated mucosa
  - Granulation tissue
  - Edematous stroma
  - Often with acute &/or chronic inflammation
- Single layer of epithelial cells may cover &/or form invaginations in fibrous stroma
  - Typical columnar biliary-type epithelium
  - Epithelium may show reactive changes or be denuded
- Clusters of pyloric-type glands may be present
  - Should not be misinterpreted as evidence of pyloric-type intracholecystic papillary/tubular neoplasm

DIFFERENTIAL DIAGNOSIS

Pyloric-Type Intracholecystic Papillary/Tubular Neoplasm

- Lesion composed of pyloric-type glands
- Lacks inflammation, ulceration, stromal edema

Cholesterol Polyp

- Localized form of cholesterolosis
- Collection of lipid-laden macrophages form polypoid mucosal lesion
- Appears yellow at gross examination
- Stroma filled with lipid-laden macrophages
- Lacks chronic inflammation and granulation tissue-type stroma of inflammatory polyp

Primary Papillary Hyperplasia

- Closely spaced villous folds that are taller than normal
  - Lacks inflammation, metaplasia changes
  - Can occur in association with metachromatic leukodystrophy
  - Lamina propria expansion by macrophages containing abnormal metachromatic material

Intestinal-Type Intracholecystic Papillary/Tubular Neoplasm

- Exhibits at least low-grade epithelial dysplasia
- Epithelium resembles that of typical colonic adenomas with enlarged, hyperchromatic nuclei showing pseudostratification

Biliary-Type Intracholecystic Papillary/Tubular Neoplasm

- Also lined by biliary-type epithelium
  - Lacks inflamed, edematous, granulation-type stroma

SELECTED REFERENCES

1. Sun, XJ, et al. Diagnosis and treatment of polypoid lesions of the gallbladder: report of 194 cases. *Hepatobiliary Pancreat Dis Int*. 2004; 3(4):591–594.
2. Owen, CC, et al. Gallbladder polyps, cholesterolosis, adenomyomatosis, and acute acalculous cholecystitis. *Semin Gastrointest Dis*. 2003; 14(4):178–188.
3. Levy, AD, et al. From the archives of the AFIP. Benign tumors and tumorlike lesions of the gallbladder and extrahepatic bile ducts: radiologic-pathologic correlation. Armed Forces Institute of Pathology. *Radiographics*. 2002; 22(2):387–413.
4. Terzi, C, et al. Polypoid lesions of the gallbladder: report of 100 cases with special reference to operative indications. *Surgery*. 2000; 127(6):622–627.

Hyperplastic Polyps

KEY FACTS

Terminology

- Polypoid growth of benign gallbladder mucosa
  - Usually in context of inflammatory process
  - Reportedly 2nd most common type of gallbladder polyp
- Metaplastic polyp, mucosal hyperplasia, inflammatory polyp, localized papillary hyperplasia
- Historically, a.k.a. metaplastic polyp, mucosal hyperplasia, inflammatory polyp, or localized papillary hyperplasia
  - Poorly defined diagnostic criteria and often used interchangeably

Etiology/Pathogenesis

- Most occur in setting of cholecystitis or cholelithiasis

Clinical Issues

- Usually incidental finding at time of cholecystectomy
- Benign with no risk of progression to dysplasia or malignancy
- Affects males and females with no age predilection

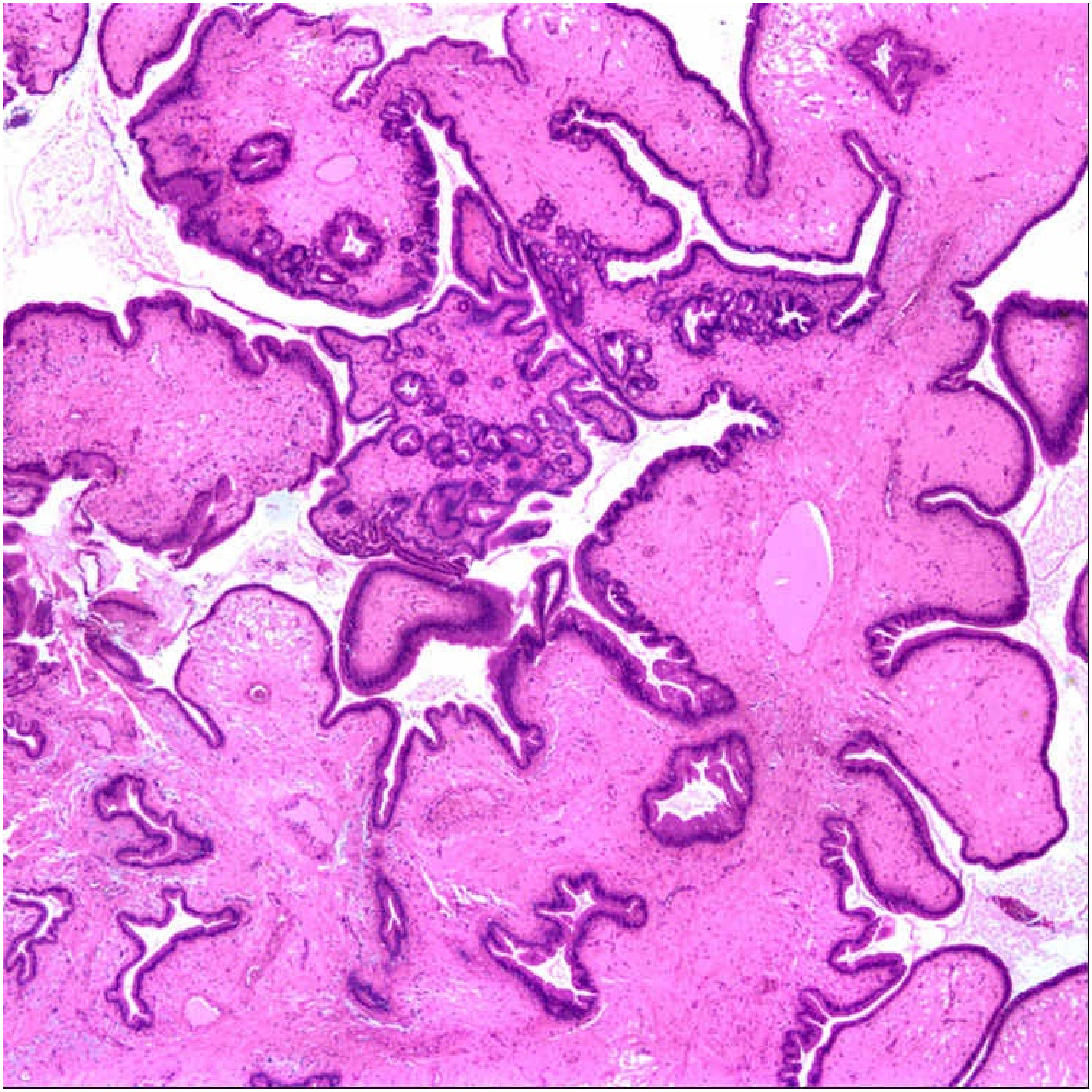
Macroscopic

- Small polyps, usually < 5 mm in diameter
- May be multiple and sessile or pedunculated

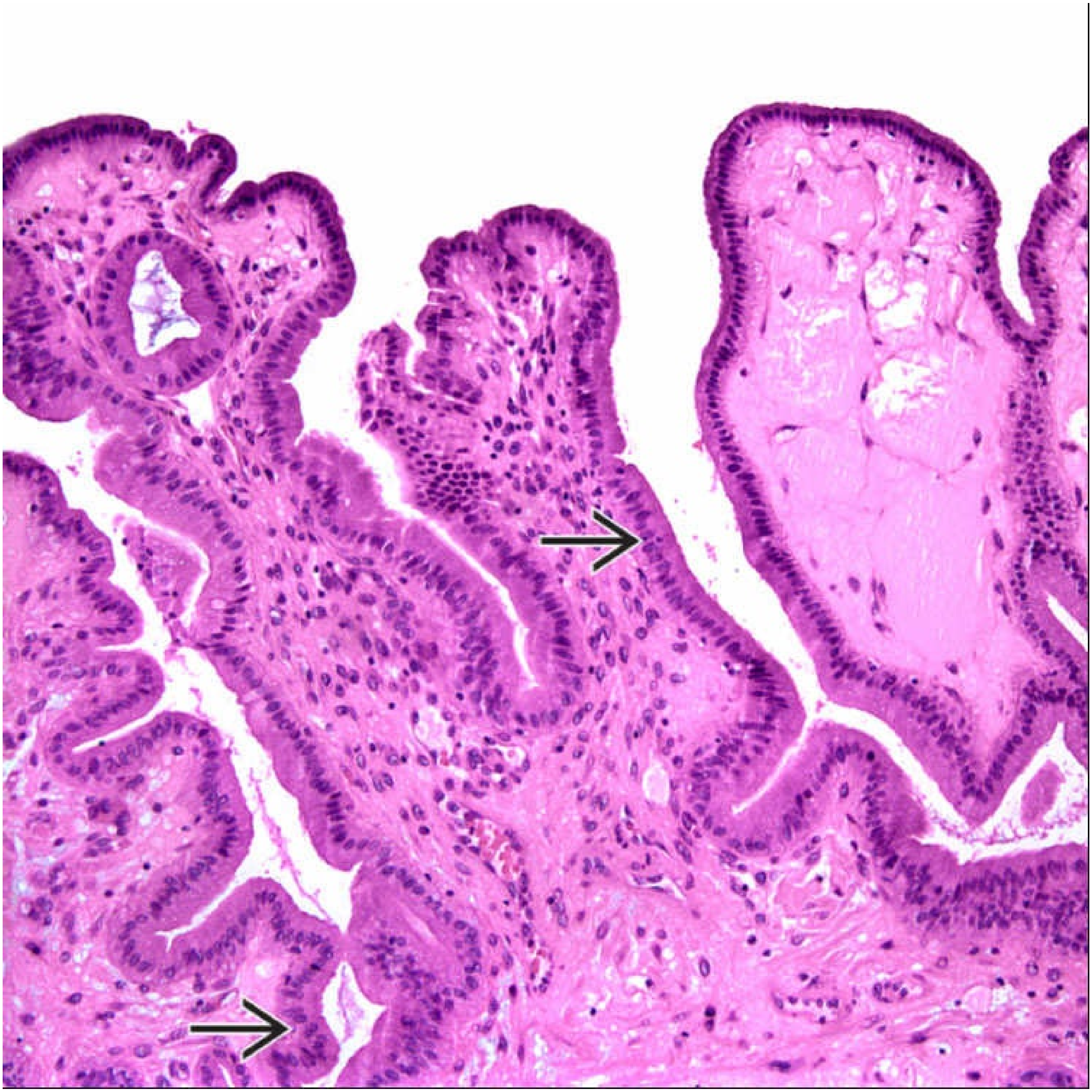
Microscopic

- Prominent hyperplastic mucosal folds and papillae
  - Mucosa on surface resembles normal gallbladder epithelium
- Metaplastic changes are common
  - Foveolar, pyloric, &/or intestinal types

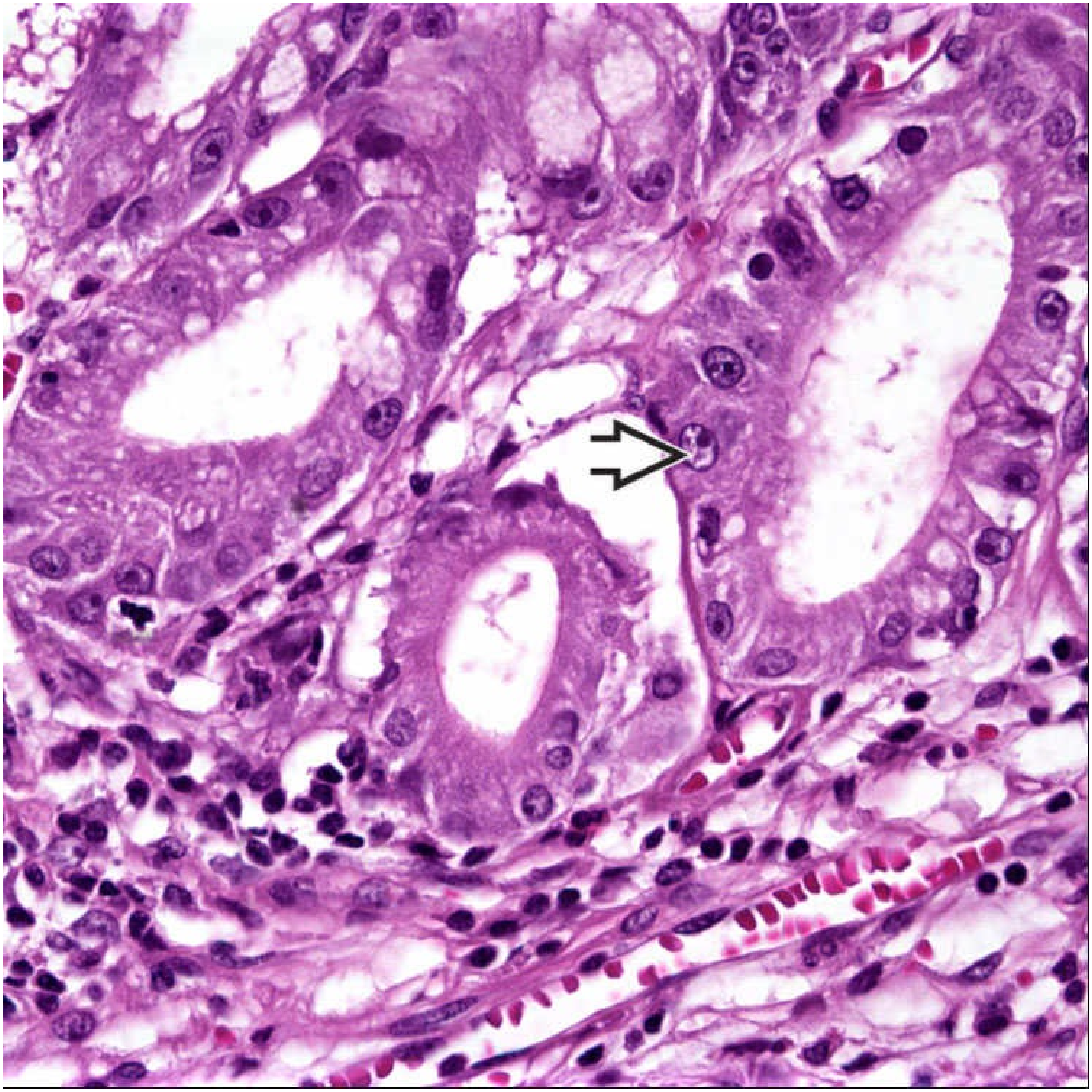
• May show focal inflammation, especially at surface
• Reactive epithelial changes may be confused with dysplasia



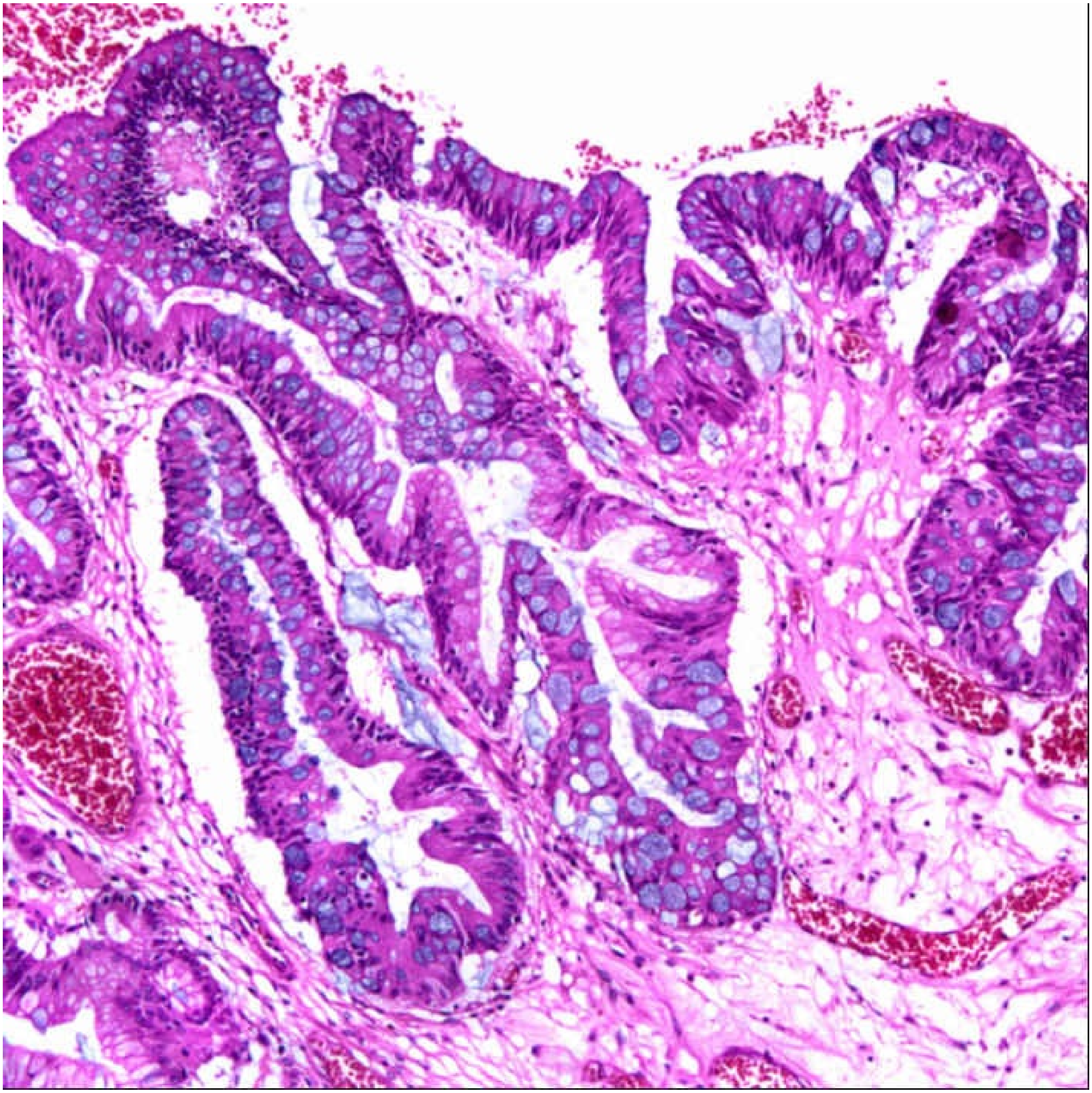
Papillary Folds and Stroma
Low-power view of a hyperplastic polyp of the gallbladder illustrates the prominent mucosal folds and papillae with abundant intervening stroma.



Benign Biliary Epithelium
H&E of a hyperplastic polyp at high power shows that the polyp surface is lined by normal-appearing gallbladder mucosa →.



Reactive Epithelial Changes
Reactive epithelial changes in a hyperplastic polyp include vesicular nuclei and prominent nucleoli
associated with inflammation.



Intestinal Metaplasia
Metaplastic changes are very common in hyperplastic polyps. This section shows intestinal-type metaplasia with many goblet cells.

TERMINOLOGY

Abbreviations

- Hyperplastic polyp (HP)

Synonyms

- Metaplastic polyp, mucosal hyperplasia, inflammatory polyp, localized papillary hyperplasia
  - Poorly defined diagnostic criteria and often used interchangeably

Definitions

- Polypoid growth of benign gallbladder mucosa, usually in context of inflammatory process

ETIOLOGY/PATHOGENESIS

Reactive/Inflammatory

- Most occur in setting of cholecystitis or cholelithiasis
- Rarely occur in association with ulcerative colitis or metachromatic leukodystrophy

CLINICAL ISSUES

Epidemiology

- Incidence
  - 2nd most common type of gallbladder polyp
  - Accounts for ~ 20% of cases, although incidence difficult to accurately assess given lack of morphologic criteria
  - Affects males and females with no age predilection

Presentation

- Usually incidental finding at time of cholecystectomy
  - May present with symptoms secondary to background cholecystitis &/or cholelithiasis

Treatment

- Surgical approaches
  - Cholecystectomy recommended if patient symptomatic or if polyp ≥ 1 cm in diameter on imaging

Prognosis

- Regarded as benign lesion with no risk of progression to dysplasia or malignancy
- Cholecystectomy is curative

IMAGING

Radiographic Findings

- Larger lesions may be detected radiographically with ultrasound or CT scan

MACROSCOPIC

General Features

- Small, polypoid mucosal lesions
  - Usually < 0.5 cm in diameter
- May be multiple
- May be either sessile or pedunculated

MICROSCOPIC

Histologic Features

- Prominent hyperplastic mucosal folds and papillae
  - Mucosa consists of typical columnar-type gallbladder epithelium
  - Metaplastic changes are common
  - Gastric-type foveolar mucosa
  - Gastric pyloric-type mucus-secreting glands
  - Intestinal-type mucosa with goblet cells, possible Paneth cells, and endocrine cells
- May show focal inflammation, especially at surface
  - Usually nonspecific chronic inflammation
    - Consists predominantly of lymphocytes with smaller numbers of plasma cells, histiocytes, eosinophils, and neutrophils
  - May be associated with reactive epithelial changes
    - May be confused with dysplasia
    - Reactive changes should be focal and accompanied by inflammation
    - Nuclei are enlarged and vesicular
    - Occasionally, nuclei may be focally pseudostratified or crowded

DIFFERENTIAL DIAGNOSIS

Intracholecystic Papillary-Tubular Neoplasms

- Multiple epithelial types that may be mixed
  - Intestinal, pyloric, biliary, gastric
  - Intestinal and biliary types have diffusely dysplastic nuclear features
  - Pyloric type composed of tightly packed pyloric type glands
- Typically 1 cm or larger
- Inflammatory component often less prominent than hyperplastic/inflammatory polyps
- Stromal component much less prominent than hyperplastic polyps

Cholesterol Polyp

- Formed by multiple lipid-laden, foamy macrophages within stroma

Diffuse Mucosal Hyperplasia

• Widespread nonpolypoid hyperplasia; not discrete lesion

Gastric Heterotopia

• Composed of pyloric-type glands with parietal and chief cells

SELECTED REFERENCES

1. Mainprize, KS, et al. Surgical management of polypoid lesions of the gallbladder. *Br J Surg*. 2000; 87(4):414–417.
2. Kubota, K, et al. Giant hyperplastic polyp of the gallbladder: a case report. *J Clin Ultrasound*. 1996; 24(4):203–206.
3. Albores-Saavedra, J, et al. Non-neoplastic polypoid lesions and adenomas of the gallbladder. *Pathol Annu*. 1993; 28(Pt 1):145–177.
4. Warfel, KA, et al. Villous papilloma of the gallbladder in association with leukodystrophy. *Hum Pathol*. 1984; 15(12):1192–1194.
5. Christensen, AH, et al. Benign tumors and pseudotumors of the gallbladder. Report of 180 cases. *Arch Pathol*. 1970; 90(5):423–432.

Cholesterol Polyps and Cholesterolosis

KEY FACTS

Terminology

- Accumulation of neutral lipid within macrophages of lamina propria of gallbladder

Etiology/Pathogenesis

- May reflect increased hepatic synthesis of lipids or increased absorption and esterification by gallbladder but pathogenesis poorly understood

Clinical Issues

- 50-60% of all gallbladder polyps
  - Prevalence of 12% in autopsy studies and from 9-26% in surgical pathology studies
- Usually asymptomatic and discovered incidentally at cholecystectomy
  - Clinical significance, if any, is unclear
- Peak in 5th and 6th decades of life

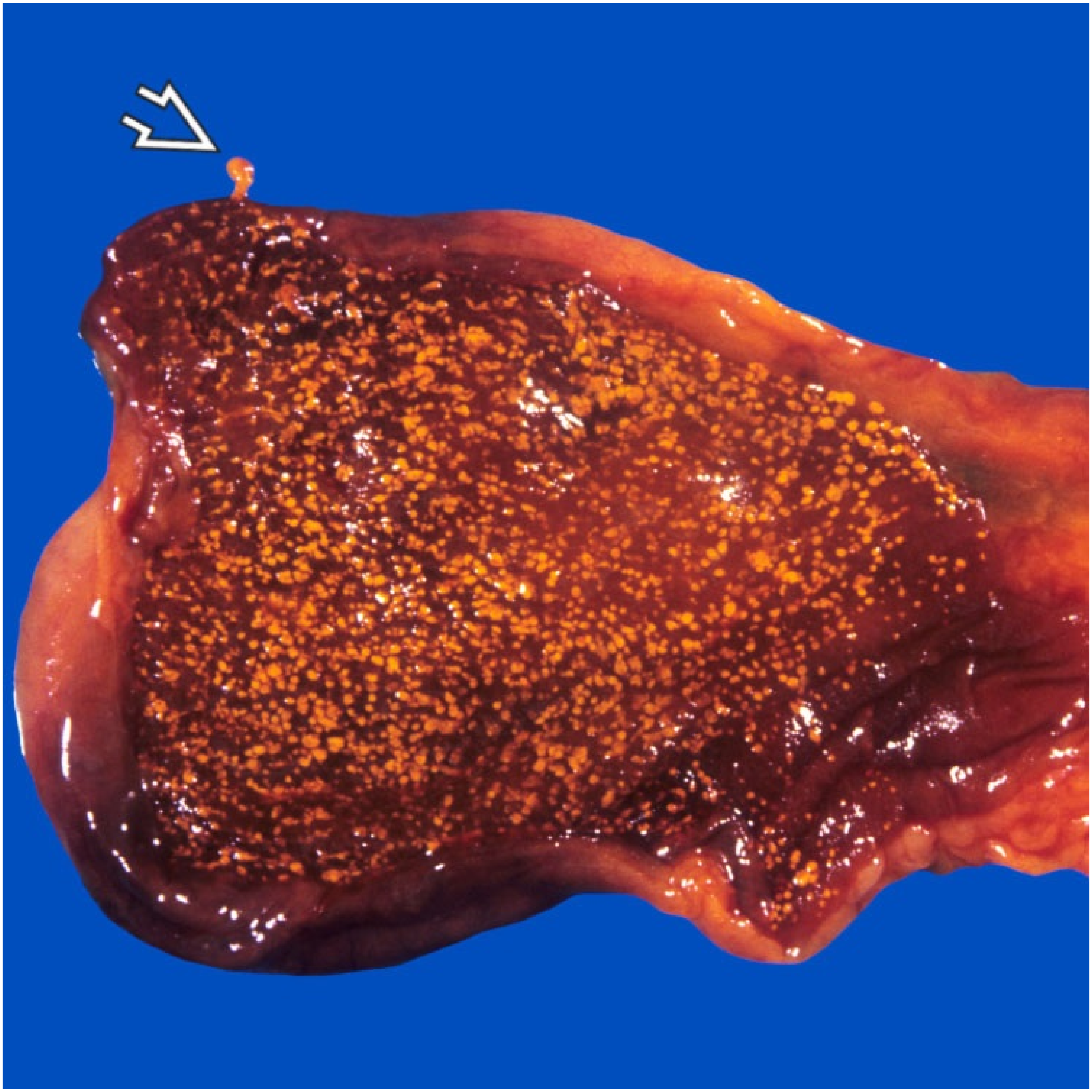
Macroscopic

- Cholesterolosis
  - Lipid droplets appear as yellow flecks or streaks against green or red background (strawberry gallbladder)
- Cholesterol polyps
  - Foamy macrophages form polypoid excrescences that project into lumen
- Diffuse cholesterolosis is most common pattern (~ 80%)
  - Mixed cholesterolosis and polyps, or polyps alone, less common (~ 10% each)

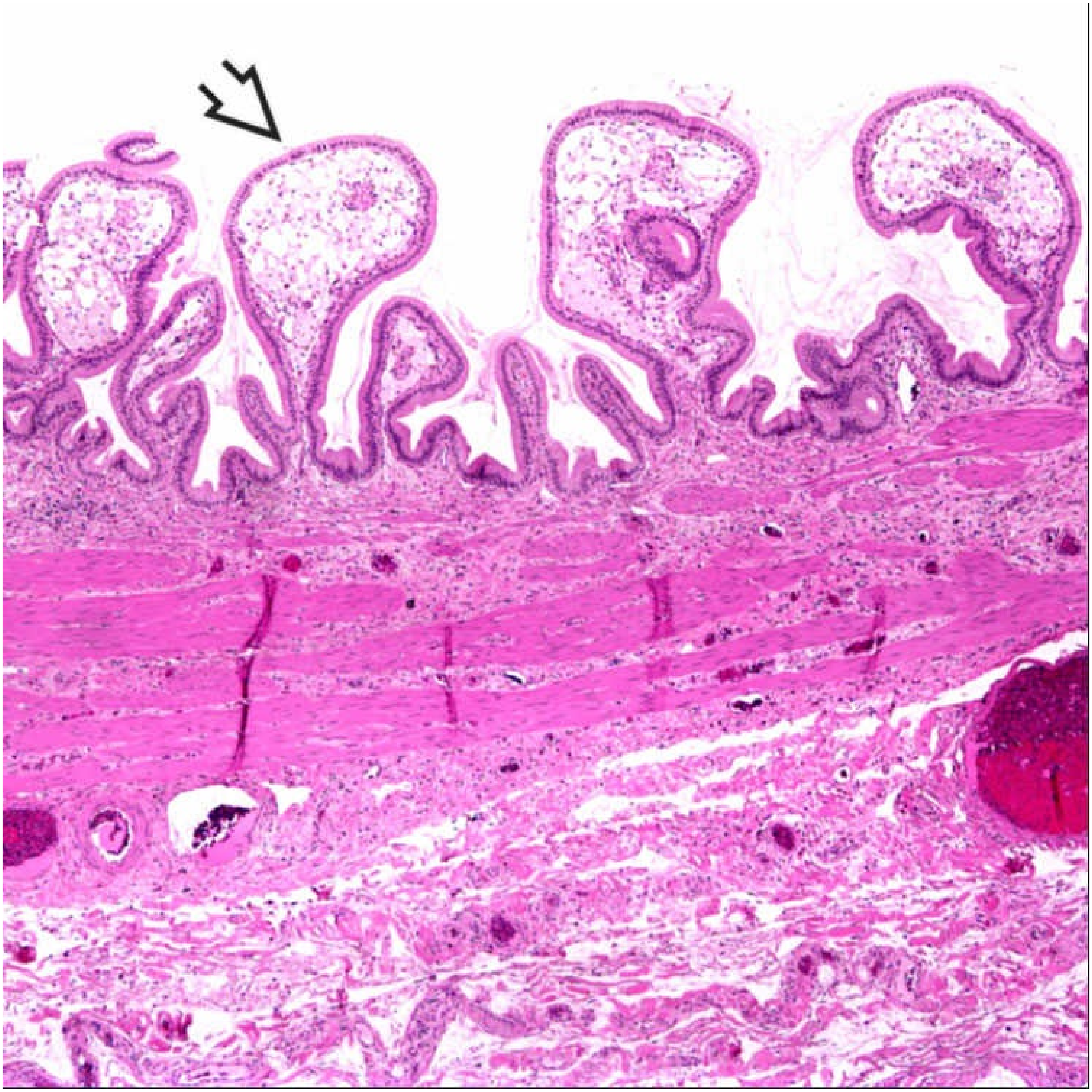
Microscopic

- Foamy macrophages with small dark nuclei accumulate in lamina propria of gallbladder mucosa
- Cholesterol polyps have lobulated architecture, vascular stalk

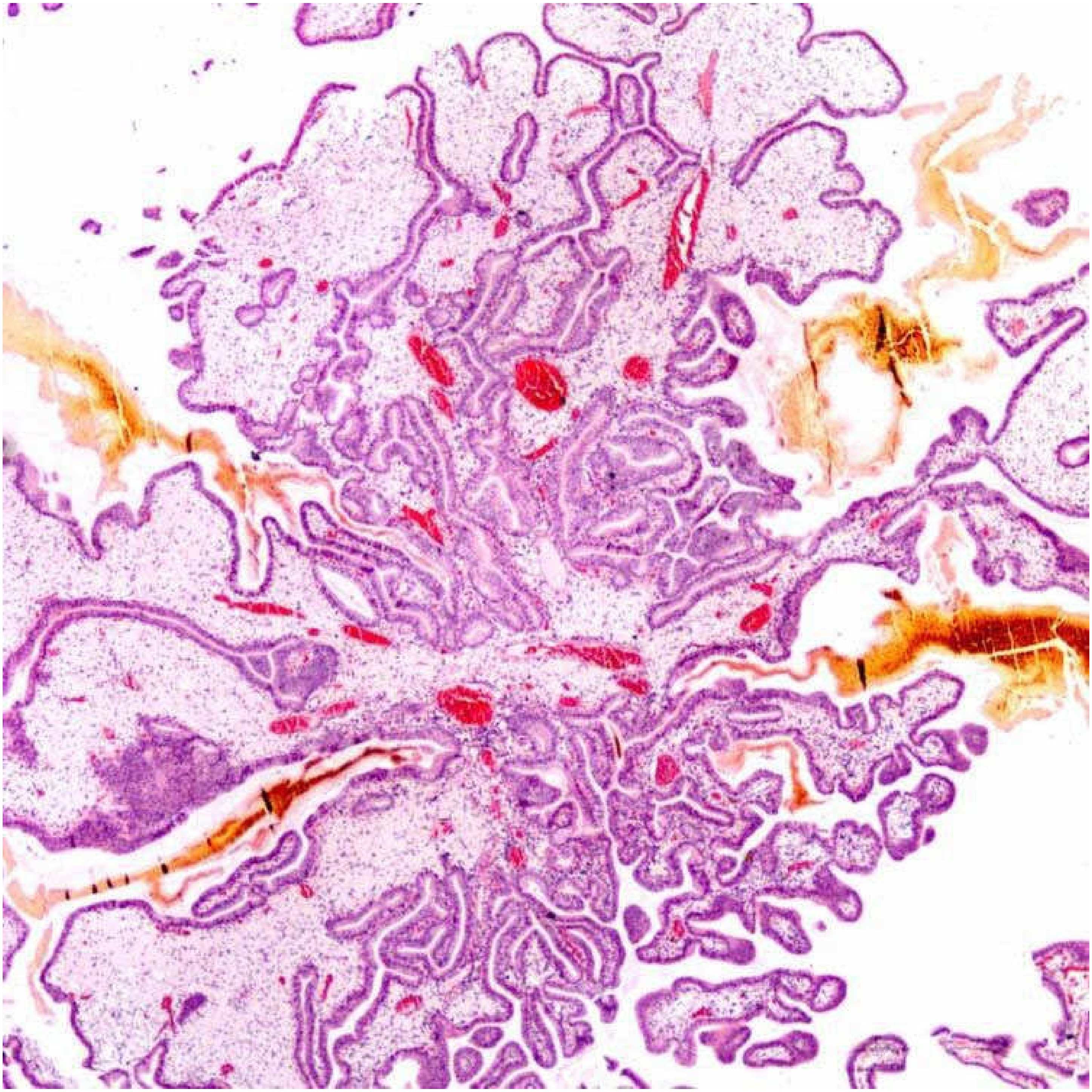
• Cholesterolosis may result in thickened folds &/or polyps
• Minimal inflammation unless there are concomitant gallstones



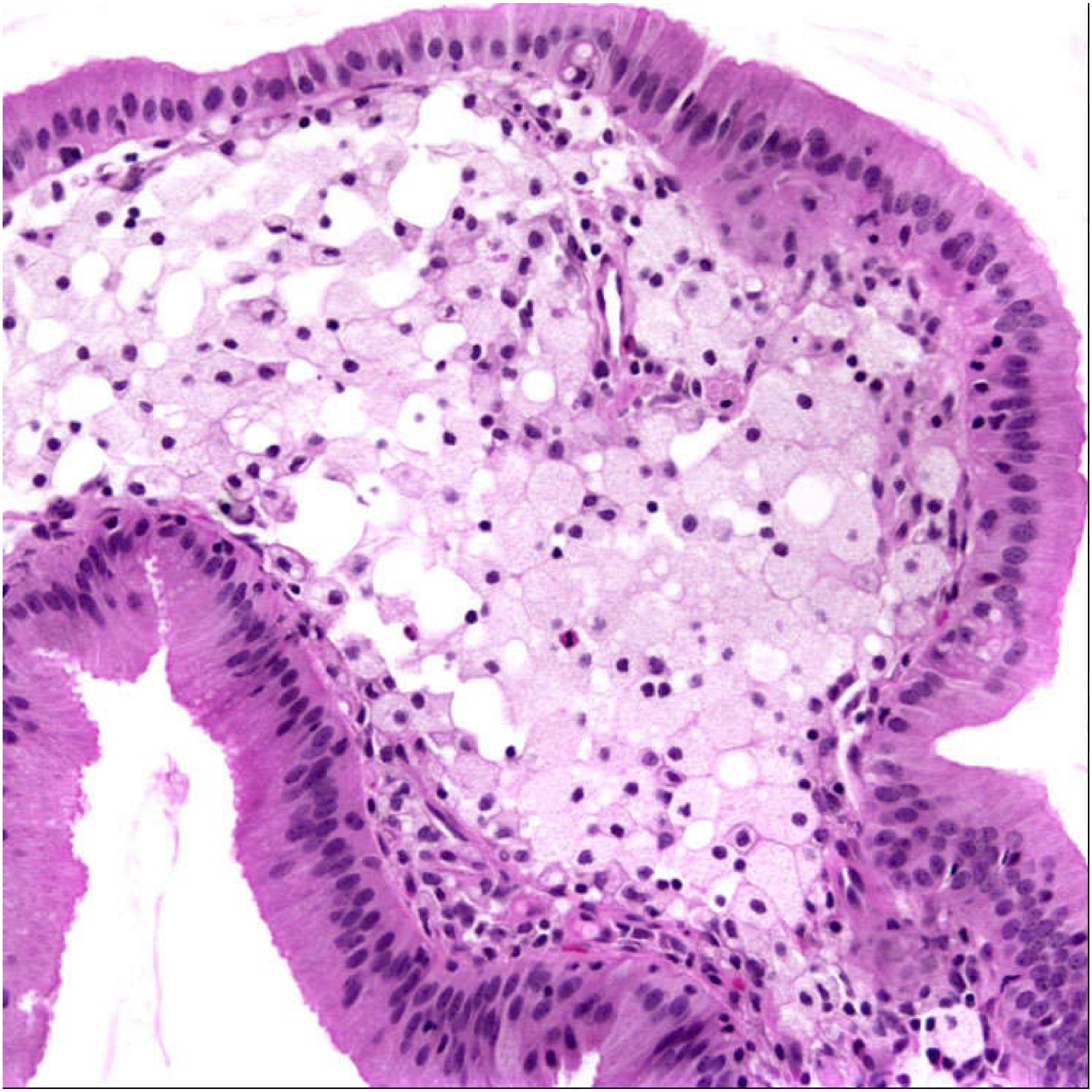
Strawberry Gallbladder
This gross photograph of a gallbladder with cholesterolosis shows numerous yellow dots against red-brown mucosa in the background, somewhat resembling a strawberry. In addition, there is a small cholesterol polyp ⇨ .



Cholesterolosis
Cholesterolosis features multiple villi with expansion of the lamina propria by numerous foamy macrophages ➩ .



Cholesterol Polyp
This large cholesterol polyp has become detached from the underlying mucosa. The polyp is composed of foamy macrophages with overlying biliary mucosa and minimal inflammation.



Foamy Macrophages
A high-power view shows expansion of a villous tip by numerous macrophages with expanded foamy clear cytoplasm. The foamy macrophages are similar in both cholesterolosis and cholesterol polyps.

TERMINOLOGY

Definitions

- Accumulation of neutral lipid within macrophages of lamina propria of gallbladder

ETIOLOGY/PATHOGENESIS

Pathogenesis

- Poorly understood
- May reflect increased hepatic synthesis of lipids or increased absorption and esterification by gallbladder
- Frequently occurs with cholesterol gallstones in setting of supersaturated bile

CLINICAL ISSUES

Epidemiology

- Incidence
  - Cholesterol polyps account for 50-60% of all gallbladder polyps
  - Prevalence rate of 12% in autopsy studies and from 9-26% in surgical studies
    – More prevalent in patients with morbid obesity
- Age
  - Usually patients between 20-70 years
  - Peak in 5th and 6th decades of life

Presentation

- Usually asymptomatic and discovered incidentally
- Occasional reports of cholesterol polyps becoming detached and impacted in distal bile duct, resulting in jaundice

Treatment

- Surgical approaches
  - Cholecystectomy

Prognosis

- Cholecystectomy is curative

IMAGING

Radiographic Findings

- Cholesterol polyps may be seen on imaging studies, but diffuse form of cholesterolosis is infrequently recognized

MACROSCOPIC

General Features

- Cholesterolosis

- Yellow flecks/streaks against green or red mucosa
  - Flecks (usually < 1.0 mm) composed of lipid droplets
  - Appearance has been compared to strawberry (strawberry gallbladder)
- Cholesterol polyps
  - Polypoid excrescences composed of lipid droplets that project into lumen
    - Small pedunculated lesions measuring 0.4-1.0 cm
    - Connected to mucosa by fine stalk, which can be easily disrupted
- 4 different patterns may be seen
  - Diffuse type
    - Majority of cases, up to 80%
  - Polypoid pattern
    - 1 or more small mucosal polyps
    - Polyps alone (no cholesterolosis) in ~ 10% of cases
  - Mixed pattern (~ 10% of cases)
    - Cholesterol polyps in background of diffuse cholesterolosis
  - Focal
    - Cholesterolosis is limited to small area of gallbladder mucosa only
- Cholesterolosis usually ends at junction with cystic duct
  - Involvement of cystic or common ducts has been reported
- Bile may be thick and tarry with detached yellow flecks consisting of masses of foam cells (lipoidic corpuscles)

MICROSCOPIC

Histologic Features

- Foamy macrophages within lamina propria
  - May result in thickened folds &/or polyps
  - Extracellular deposits of lipid are rare
  - Macrophages have small dark nuclei and foamy cytoplasm
- Cholesterol polyps
  - Vascular connective tissue stalk
  - Lobulated architecture with variable number of branching villous projections
  - Packed with numerous foamy macrophages of type seen in diffuse form of cholesterolosis
  - Overlying histologically unremarkable biliary epithelium
- Lipofuscin pigment may be present in small number of patients
  - Can be within histiocytes as well as adjacent gallbladder epithelium
  - Brownish, granular pigment that is weakly PAS(+)
  - Most likely related to leakage of bile into mucosa
- Minimal inflammation unless gallstones present

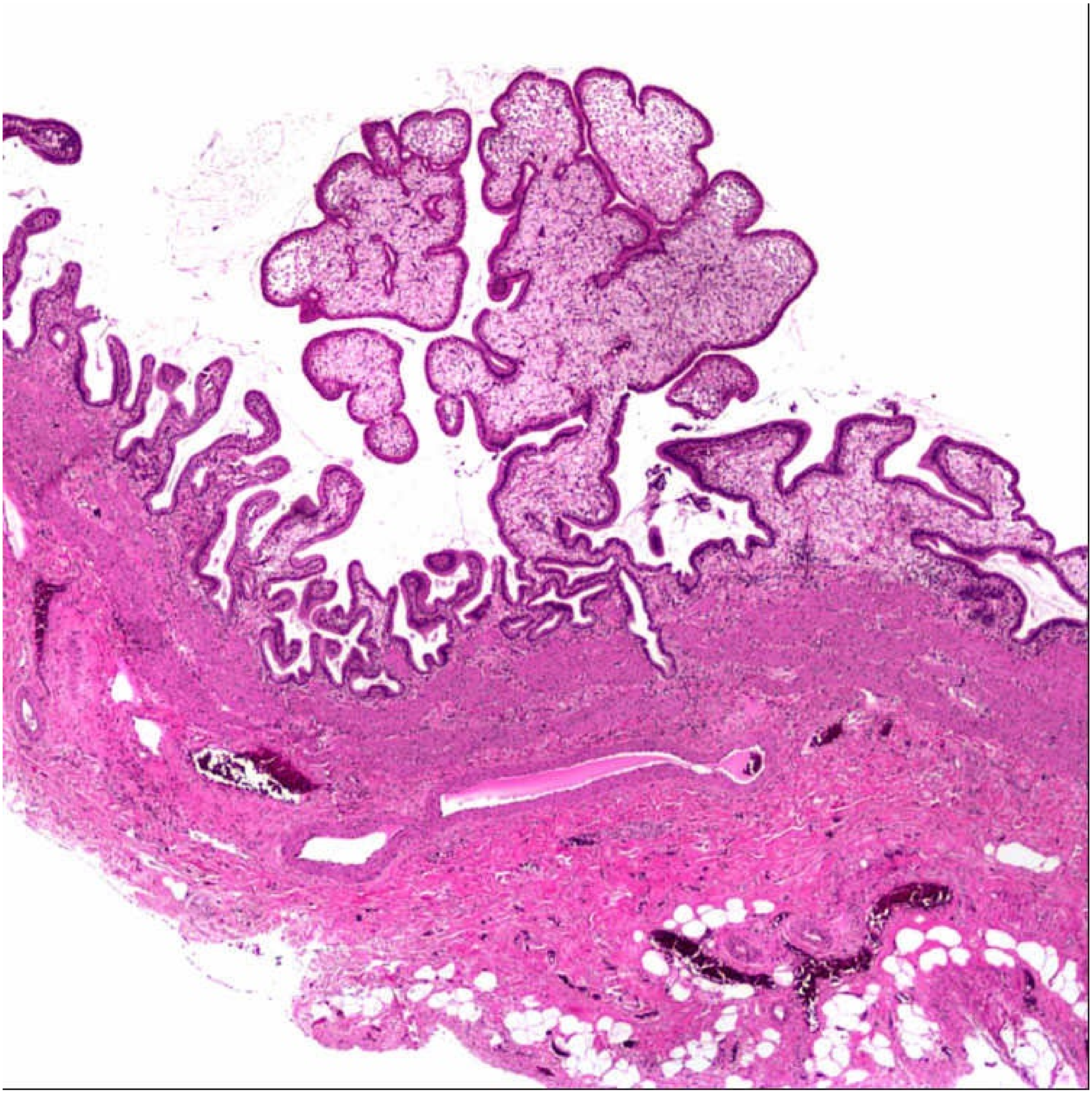
DIFFERENTIAL DIAGNOSIS

Metachromic Leukodystrophy

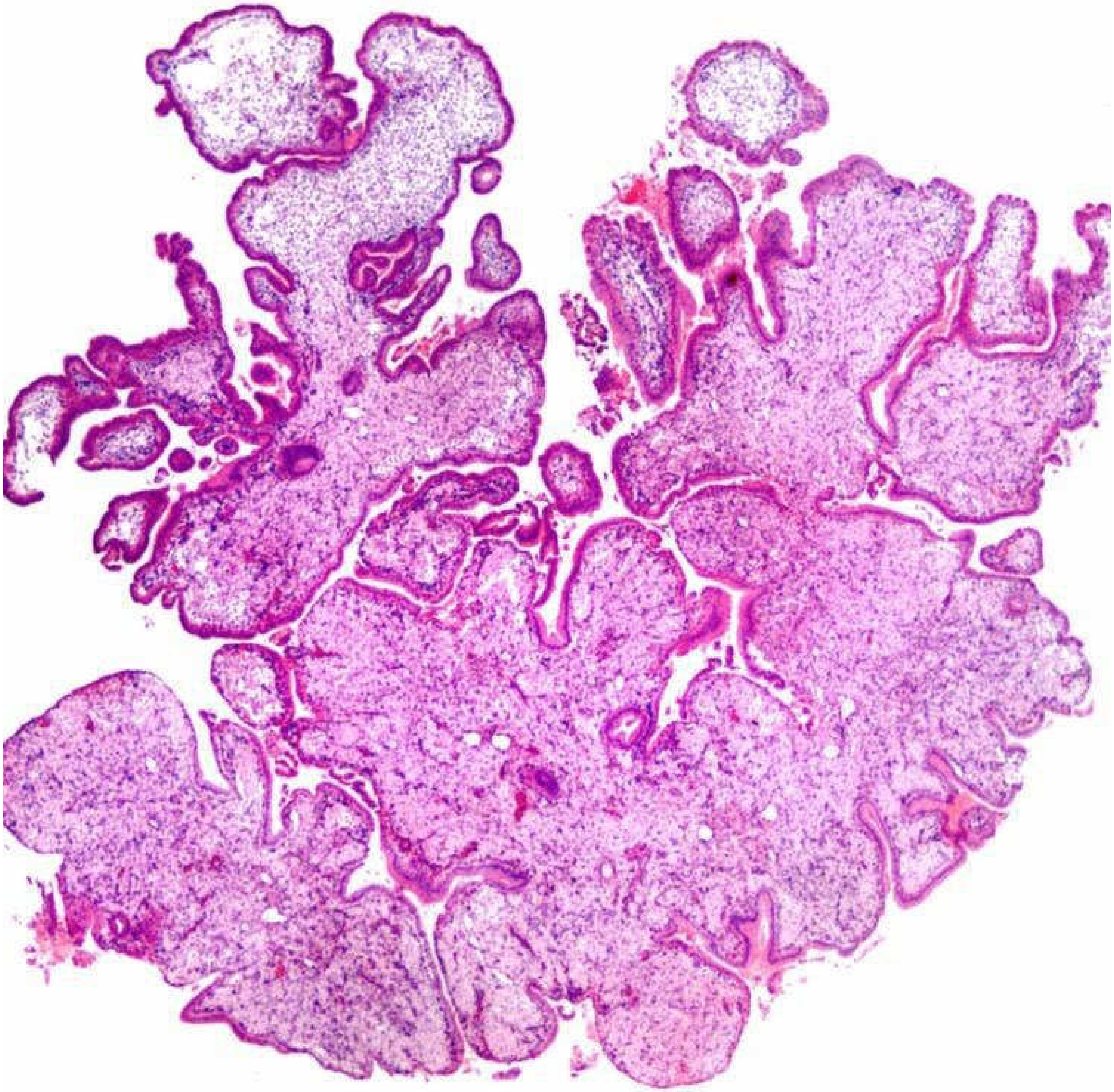
- Macrophages contain brown-tan material, not cholesterol
- Occurs in infants and young children with significant neurological symptoms

Hyperplastic or Inflammatory Polyp

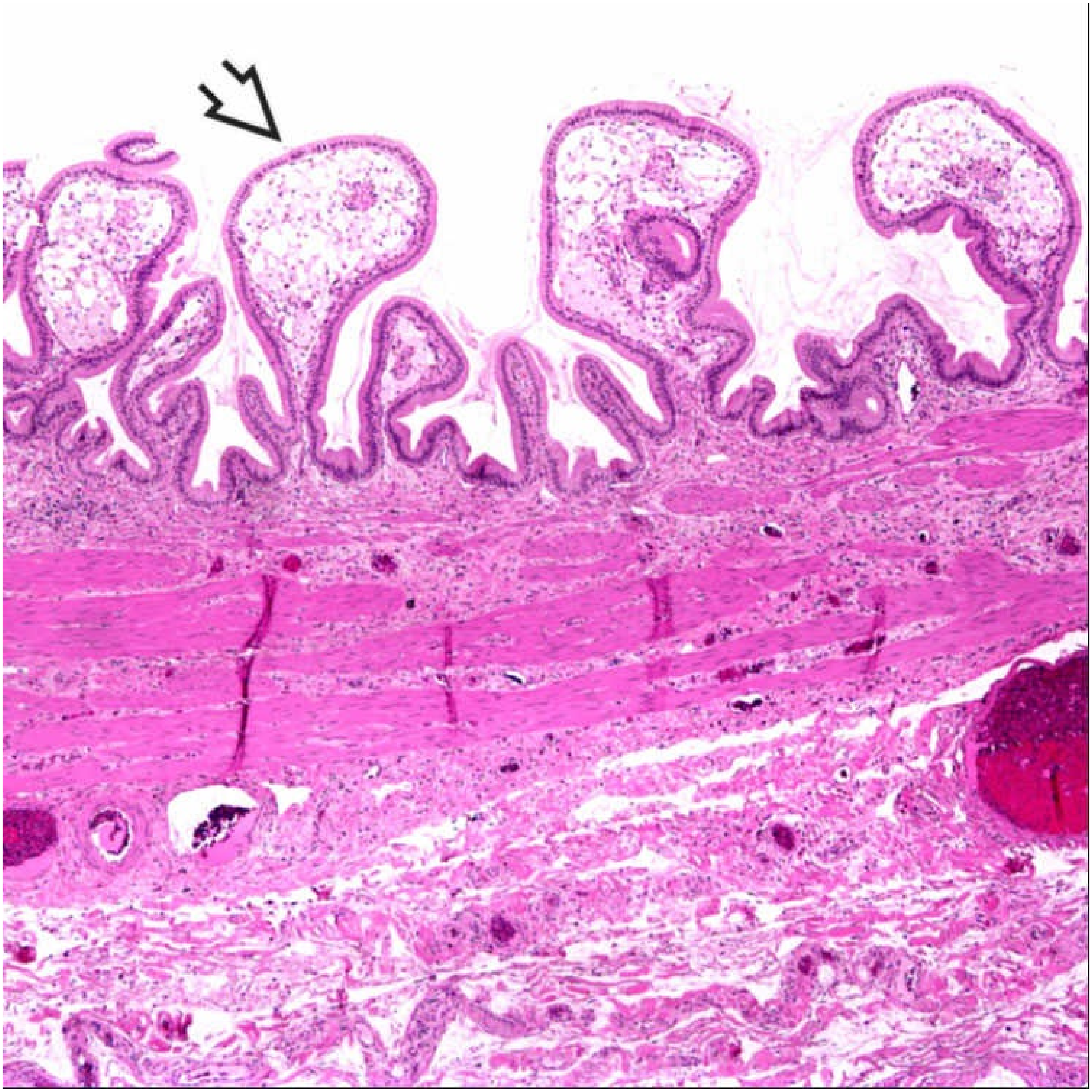
- No lipid-filled macrophages, inflammation often present



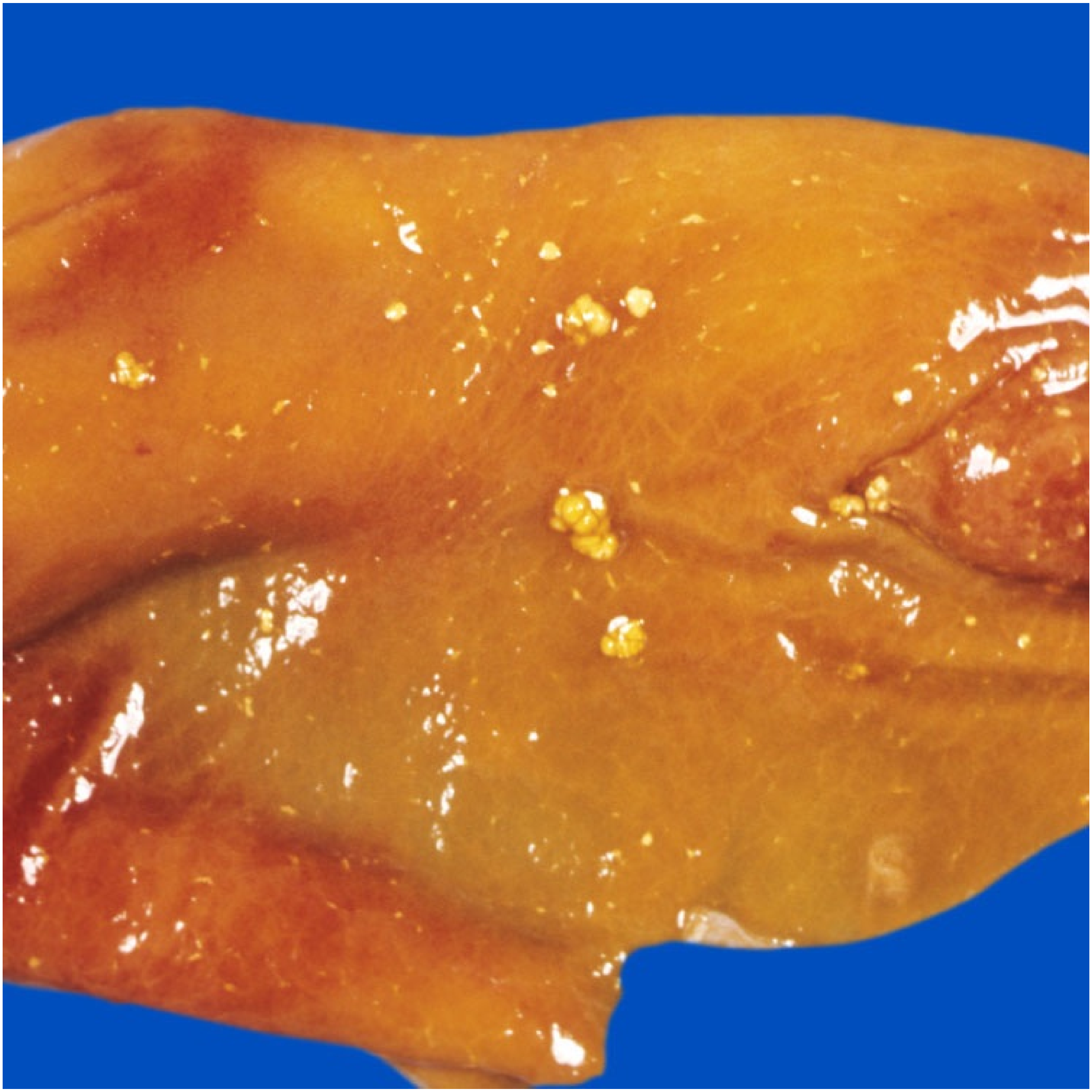
A small, lobulated cholesterol polyp is arising from the gallbladder mucosa.



This lobulated cholesterol polyp has become detached from the underlying mucosa. Note the prominent foamy macrophages and minimal inflammation.



Cholesterolosis features multiple villi with expansion of the lamina propria by numerous foamy macrophages ➩ .



A few lobulated cholesterol polyps are seen in a cholecystectomy specimen, along with a few mucosal yellow streaks indicative of a background of cholesterolosis.

SELECTED REFERENCES

1. Dairi, S, et al. Implications of gallbladder cholesterolosis and cholesterol polyps? *J Surg Res*. 2016; 200(2):467–472.
2. Sandri, L, et al. Gallbladder cholesterol polyps and cholesterolosis. *Minerva Gastroenterol Dietol*. 2003; 49(3):217–224.
3. Jacyna, MR, et al. Cholesterolosis: a physical cause of “functional” disorder. *Br Med J (Clin Res Ed)*. 1987; 295(6599):619–620.
4. Salmenkivi, K. Cholesterosis of the gallbladder. Surgical considerations. *Int Surg*. 1966; 45(3):304–309.

5. Salmenkivi, K. Cholersterosis of the gall-bladder. A clinical study based on 269 cholecystectomies. *Acta Chir Scand*. 1964; Suppl. 105(suppl 324):1–93.
6. Feldman, M, et al. Cholesterosis of the gallbladder; an autopsy study of 165 cases. *Gastroenterology*. 1954; 27(5):641–648.

SECTION 5
TUMORS OF THE PANCREAS

OUTLINE

Pancreatic Intraepithelial Neoplasia

KEY FACTS

Terminology

- Noninvasive pancreatic intraductal epithelial proliferation, likely precursor of pancreatic ductal adenocarcinoma

Clinical Issues

- High-grade PanIN indicates elevated risk for pancreatic adenocarcinoma
- High-grade PanIN at surgical margin may warrant further resection, but some reports have suggested no adverse consequence of PanIN-3 at resection margin
- Low-grade PanIN: Commonly found in resected pancreas; significance unclear
- High-grade PanIN occurs concurrently with ductal adenocarcinoma, rarely (< 5%) in association with chronic pancreatitis and benign cysts

Microscopic

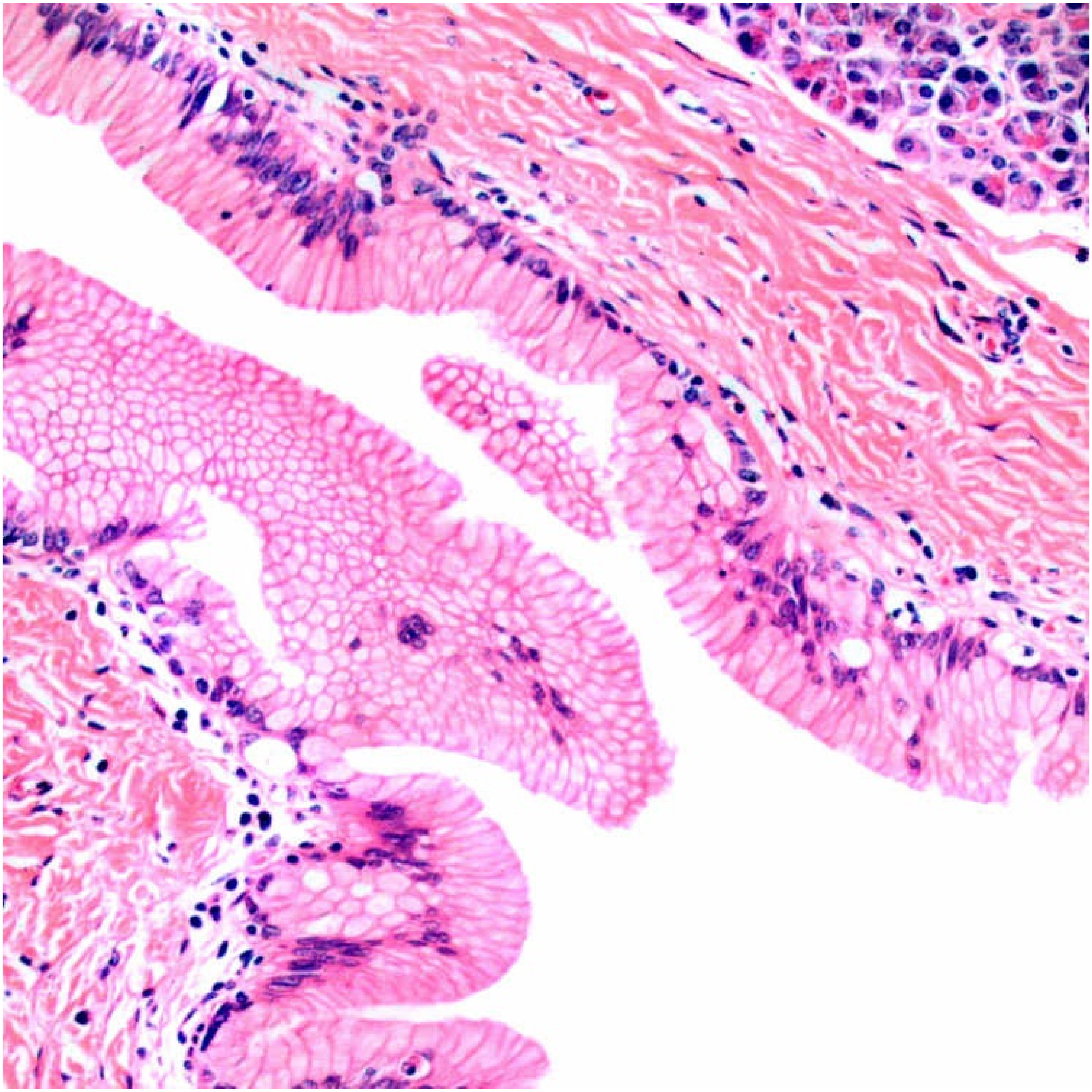
- Involved ducts are typically <5 mm in diameter
  - Former 3-tier system replaced by 2-tier scheme: Low grade and high grade
  - Low grade includes PanIN-1 and PanIN-2
  - High grade includes PanIN-3 and carcinoma in situ
- Low grade: Mild to moderate nuclear atypia
- High grade: Marked nuclear atypia, loss of polarity, cribriforming, luminal necrosis

Top Differential Diagnoses

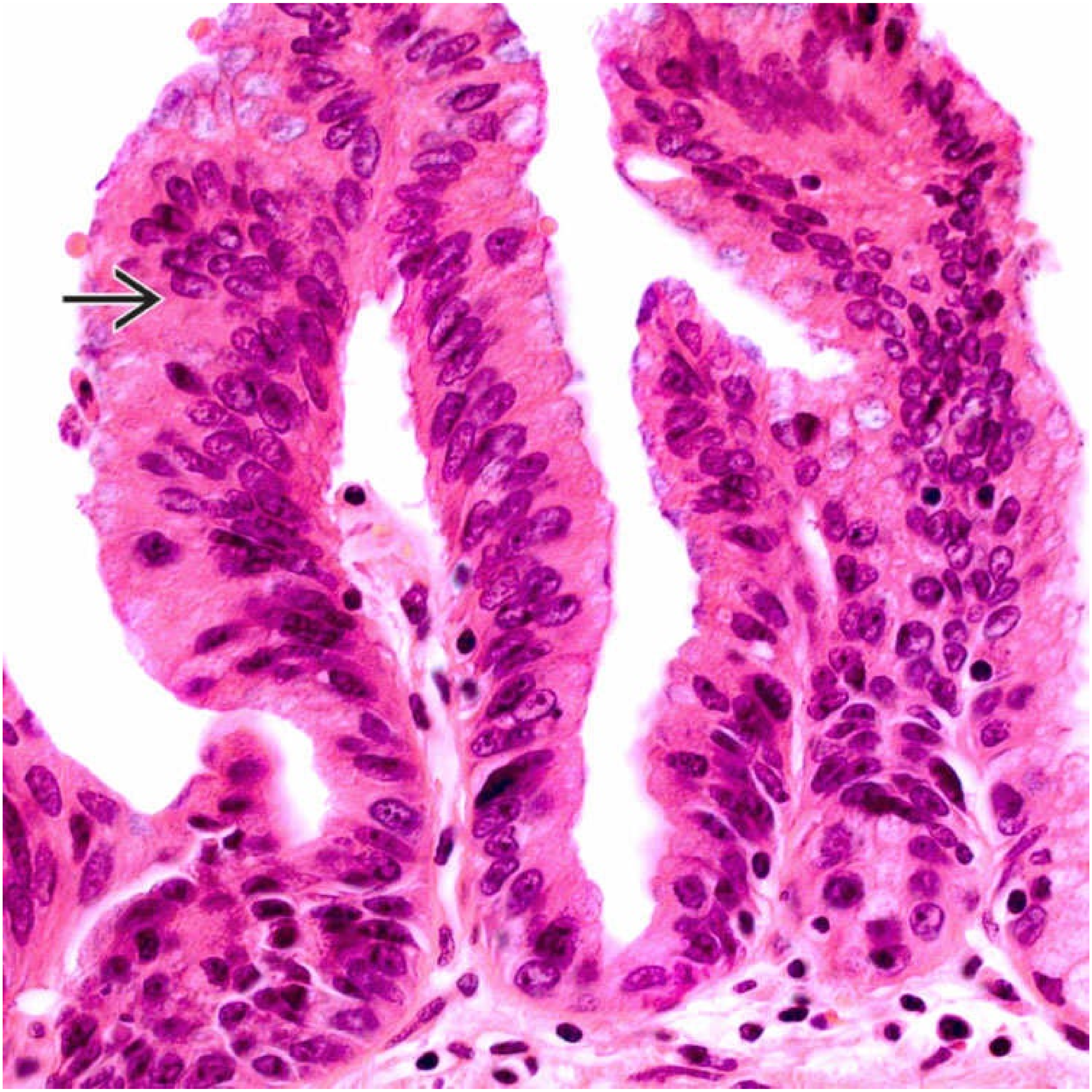
- Intraductal papillary mucinous neoplasm
- Reactive ductal epithelial changes
- Intraductal spread of invasive carcinoma (cancerization of ducts)

Diagnostic Checklist

- High-grade PanIN should be noted in pathology reports, especially in absence of invasive carcinoma
- Low-grade PanIN does not need to be reported, does not affect surgical management

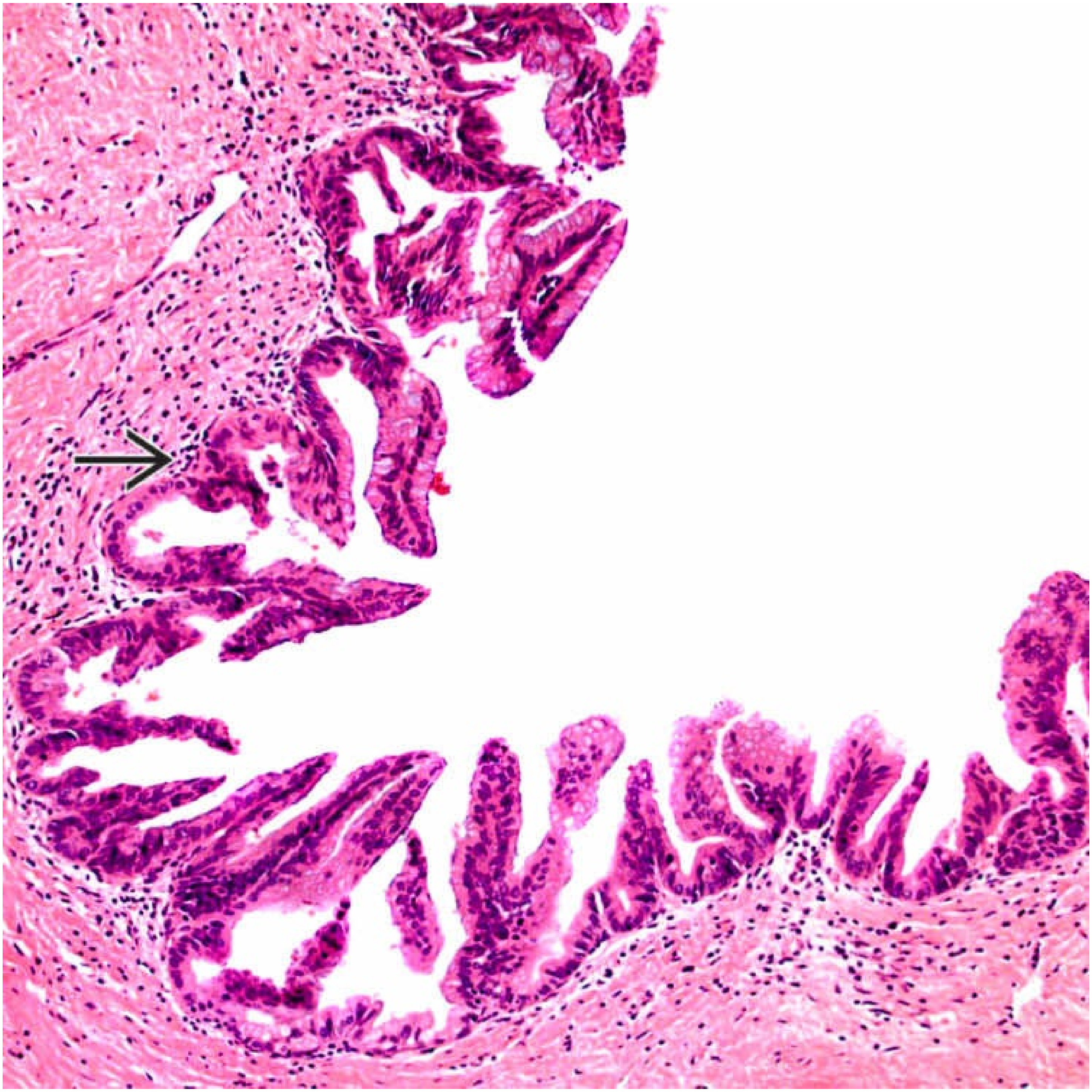


Low Grade (PanIN-1)
Pancreatic duct lined by a single layer of epithelium is shown with abundant apical mucinous cytoplasm and basal nuclei that lack atypia [formerly pancreatic intraepithelial neoplasia (PanIN)-1a].



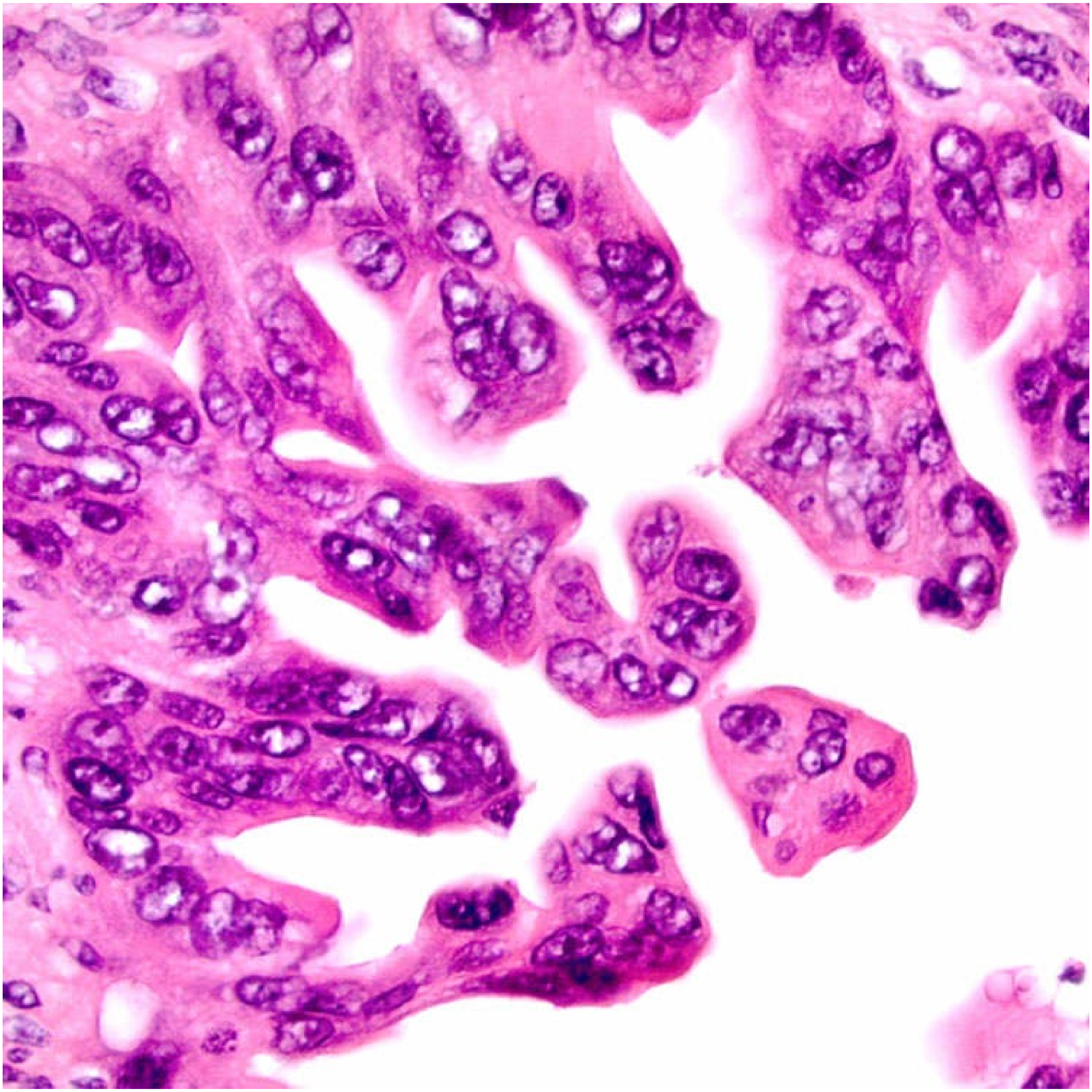
Low Grade (PanIN-2)

The lining cells show enlarged hyperchromatic nuclei and a slight loss of nuclear polarity →. The cytologic atypia distinguishes it from PanIN-1. Both PanIN-1 and PanIN-2 are now classified as low-grade PanIN.



Low-grade PanIN, Micropapillary Pattern

Pancreatic duct lined by a micropapillary proliferation of mucinous epithelial cells →. There is nuclear crowding and hyperchromasia indicating low-grade PanIN. This was formerly referred to as PanIN-2.



High-Grade PanIN
The pancreatic duct is lined by epithelial cells with micropapillary architecture, prominent cytologic atypia, variably prominent nucleoli, and loss of polarity (formerly referred to as PanIN-3).

TERMINOLOGY

Abbreviations

- Pancreatic intraepithelial neoplasia (PanIN)

Synonyms

- Dysplasia, carcinoma in situ

Definitions

- Noninvasive pancreatic intraductal epithelial proliferation, likely precursor of pancreatic ductal adenocarcinoma

ETIOLOGY/PATHOGENESIS

Molecular Progression

- Early: Telomerase shortening, *KRAS2* activation
- Intermediate: Inactivation of p16/ *CDKN2A*
- Late: Inactivation of *TP53*, *DPC4* / *SMAD4*
- p16 inactivation is seen in ~ 30-50% low-grade, 70% high grade, 95% ductal adenocarcinomas
- *KRAS* mutation is seen in ~ 40-80% low-grade, > 80% high-grade, > 90% ductal adenocarcinomas

CLINICAL ISSUES

Natural History

- Low-grade PanIN: Commonly found in resected pancreas; significance unclear
- High-grade PanIN: Associated with significant risk of progression to pancreatic ductal adenocarcinoma

Treatment

- Management of isolated high-grade PanIN not established
- Surveillance of these patients is advocated
- High-grade PanIN at surgical margin may warrant further resection

Incidence

- Low-grade PanIN sharply increases after age 40
- High-grade PanIN occurs concurrently with ductal adenocarcinoma, rarely (< 5%) in association with chronic pancreatitis and benign cysts

IMAGING

General Features

- PanIN lesions are typically very small and thus radiologically undetectable

MACROSCOPIC

General Features

- Not visible grossly

MICROSCOPIC

Histologic Features

- Involved ducts are typically < 5 mm in diameter
  - Both main pancreatic duct and peripheral pancreatic lobules may be involved
  - Often multifocal with admixed grades
- Flat or papillary, occasionally complex architectural patterns
- Often abundant supranuclear mucin without intraluminal mucin

Grading PanIN

- Former 3-tier system replaced by 2-tier scheme: Low grade and high grade
  - Low grade includes PanIN-1 and PanIN-2
  - High grade includes PanIN-3 and carcinoma in situ
- Low grade (PanIn-1)
  - Nuclei are small, lack nuclear atypia
  - Tall columnar epithelium with basal nuclei and abundant supranuclear mucin
  - Flat (PanIN-1A) or papillary/micropapillary (PanIN-1B)
- Low grade (PanIN-2)
  - Generally papillary, occasionally flat
  - Mild to moderate nuclear atypia
    - Nuclear crowding, enlargement, pseudostratification, hyperchromasia
    - No atypical mitoses
- High grade (PanIN-3)
  - Usually papillary and micropapillary
  - Cribriforming, budding, luminal necrosis
  - Marked nuclear atypia, loss of polarity, macronucleoli, frequent mitoses
- Histologic variants
  - Intestinal type: Goblet cells and nuclear pseudostratification
  - Foamy cell type: Cells with foamy cytoplasm
  - Oncocytic type: Abundant granular cytoplasm with prominent nucleoli
- PanIN may be surrounded by parenchymal atrophy (lobulocentric atrophy)
- Multifocal lobulocentric atrophy common in patients with family history of pancreatic cancer

DIFFERENTIAL DIAGNOSIS

Intraductal Papillary Mucinous Neoplasm

- Usually > 1 cm, visible lesion on imaging favors itraductal papillary mucinous neoplasm (IPMN)
- Papillae taller and more complex
- “Incipient IPMN” proposed for lesions 0.5-1.0 cm with intestinal/oncocytic features or *GNAS* mutation

Reactive Ductal Epithelial Changes

- Associated with inflammation
- Usually lack significant architectural atypia

Intraductal Spread of Invasive Carcinoma (Cancerization of Ducts)

- Spread of invasive carcinoma along preexisting ducts
- Abrupt transition from normal to markedly atypical epithelium
- Continuity of carcinoma with involved duct

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- High-grade PanIN should be noted in pathology reports, especially in absence of invasive carcinoma
- At frozen section, high-grade PanIN should be reported
- Some studies do not show adverse consequence of high-grade PanIN at resection margin
- Low-grade Pan-IN does not need to be reported, does not affect surgical management

SELECTED REFERENCES

1. Basturk, O, et al. A revised classification system and recommendations from the Baltimore Consensus Meeting for Neoplastic Precursor Lesions in the Pancreas. *Am J Surg Pathol*. 2015; 39(12):1730–1741.
2. Matthaei, H, et al. Presence of pancreatic intraepithelial neoplasia in the pancreatic transection margin does not influence outcome in patients with R0 resected pancreatic cancer. *Ann Surg Oncol*. 2011; 18(12):3493–3499.
3. Sipos, B, et al. Pancreatic intraepithelial neoplasia revisited and updated. *Pancreatology*. 2009; 9(1-2):45–54.
6. Hruban, RH, et al. An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. *Am J Surg Pathol*. 2004; 28(8):977–987.

4. Singh, M, et al. Precursor lesions of pancreatic cancer: molecular pathology and clinical implications. *Pancreatology*. 2007; 7(1):9–19.
5. Brune, K, et al. Multifocal neoplastic precursor lesions associated with lobular atrophy of the pancreas in patients having a strong family history of pancreatic cancer. *Am J Surg Pathol*. 2006; 30(9):1067–1076.
7. Andea, A, et al. Clinicopathological correlates of pancreatic intraepithelial neoplasia: a comparative analysis of 82 cases with and 152 cases without pancreatic ductal adenocarcinoma. *Mod Pathol*. 2003; 16(10):996–1006.
8. Maitra, A, et al. Multicomponent analysis of the pancreatic adenocarcinoma progression model

using a pancreatic intraepithelial neoplasia tissue microarray. *Mod Pathol*. 2003; 16(9):902–912.
9. Hruban, RH, et al. Pancreatic intraepithelial neoplasia: a new nomenclature and classification system for pancreatic duct lesions. *Am J Surg Pathol*. 2001; 25(5):579–586.

Ductal Adenocarcinoma, Including Variants

KEY FACTS

Terminology

- Adenocarcinoma arising in pancreatic ductal system
    - Comprises 85-90% of all pancreatic neoplasms

Clinical Issues

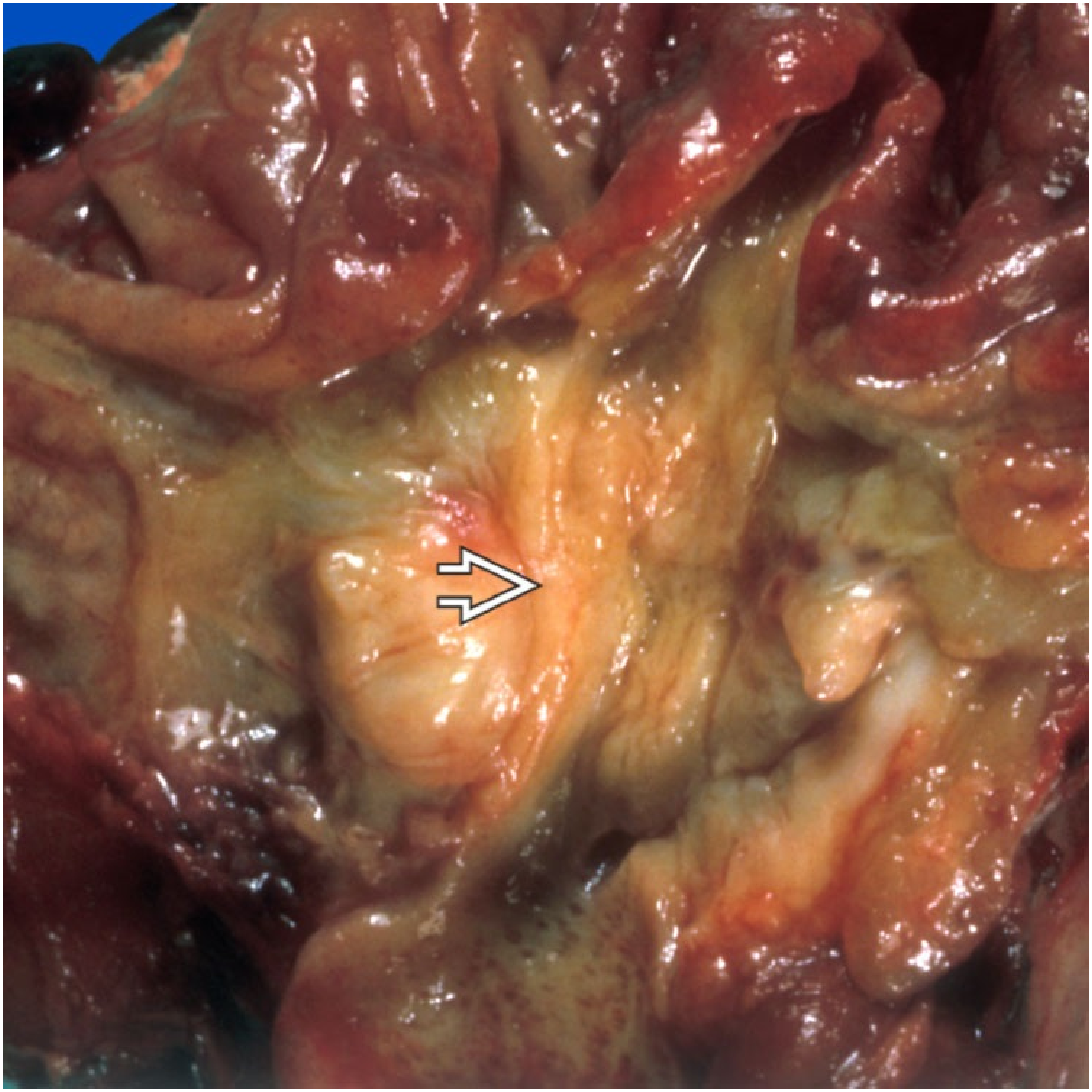
- Most cases unresectable at presentation
- Nonspecific symptoms often mean delay in diagnosis

Macroscopic

- Majority in head of pancreas
    - Poorly defined, firm mass with intense fibrotic reaction
    - Carcinoma may be difficult to distinguish from background pancreatitis

Microscopic

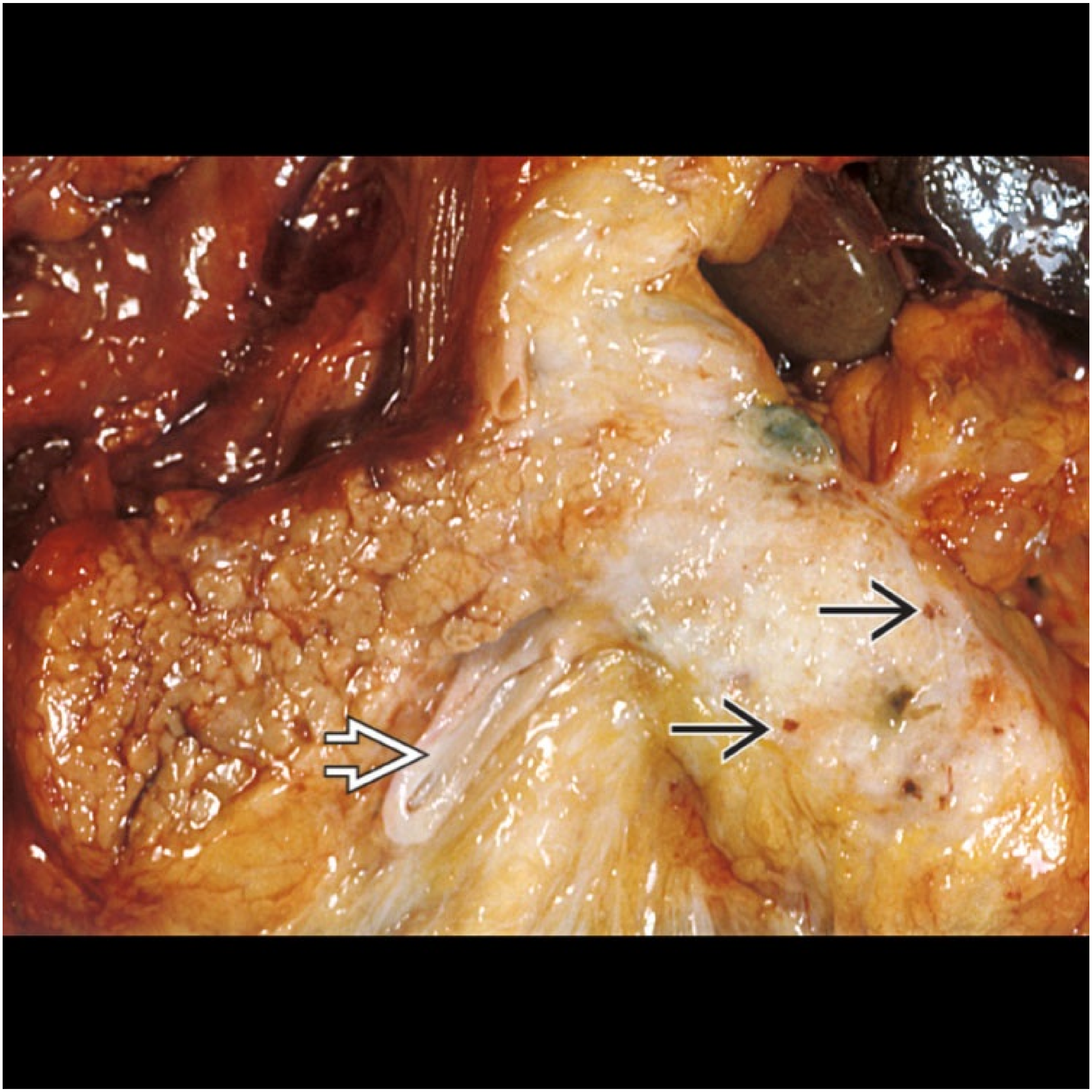
- Small, haphazardly infiltrating glands embedded in dense desmoplastic stroma
    - Perineural and angiolymphatic invasion and associated chronic pancreatitis are very common
    - Histologic patterns: Foamy gland pattern, large duct pattern
    - Histologic variants
    - Colloid carcinoma, adenosquamous, clear cell, signet ring, medullary, hepatoid, undifferentiated, carcinomas with mixed differentiation
- Immunohistochemistry
    - Cytokeratins 7, 8, 18, 19
    - CEA, CA19-9, CA125, B72.3
    - MUC1, MUC4, MUC5AC, and MUC6 (25%)



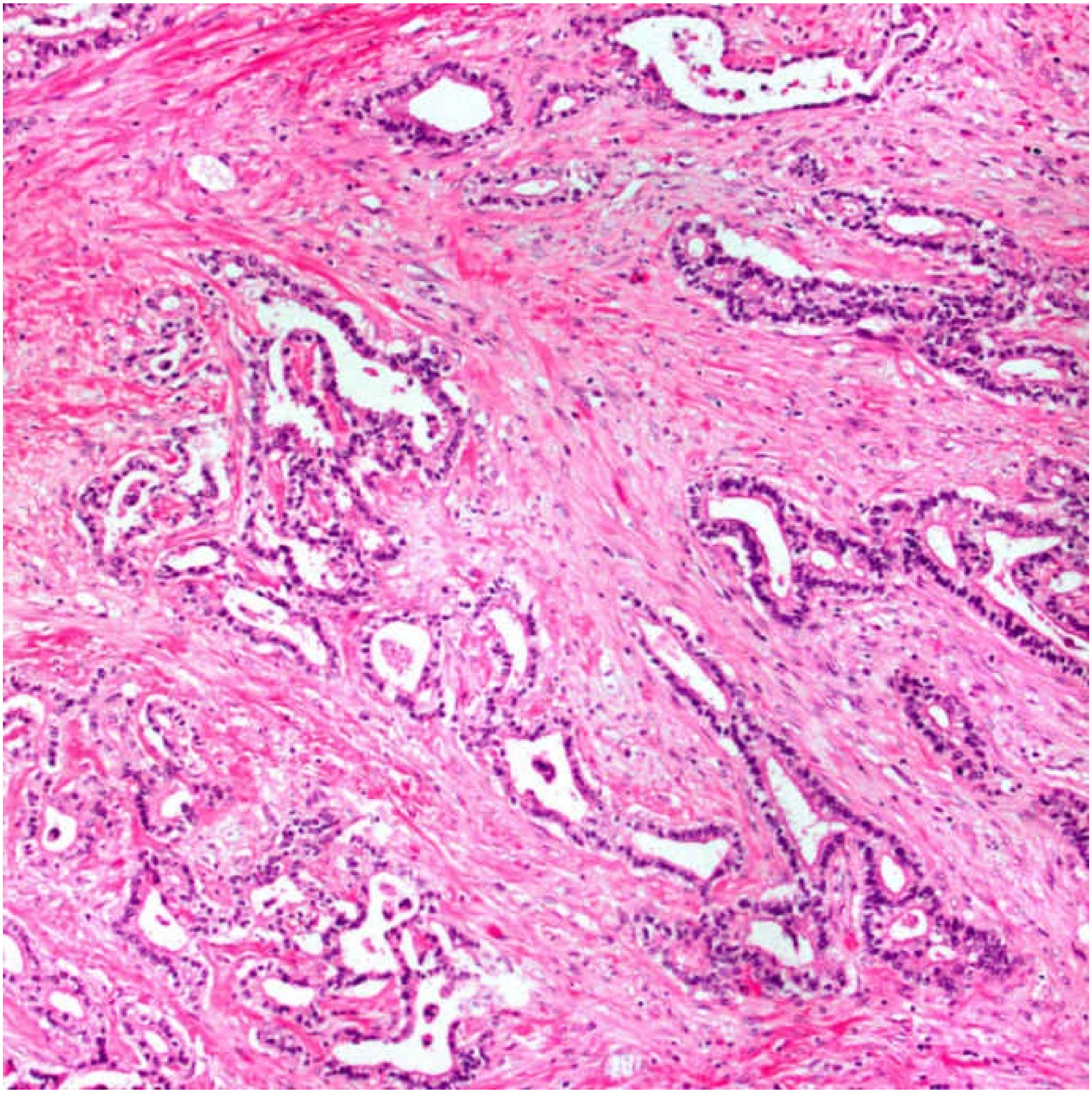
Pancreatic Ductal Adenocarcinoma

A large pancreatic mass is encroaching on the duodenum with the ampulla of Vater overlying the mass

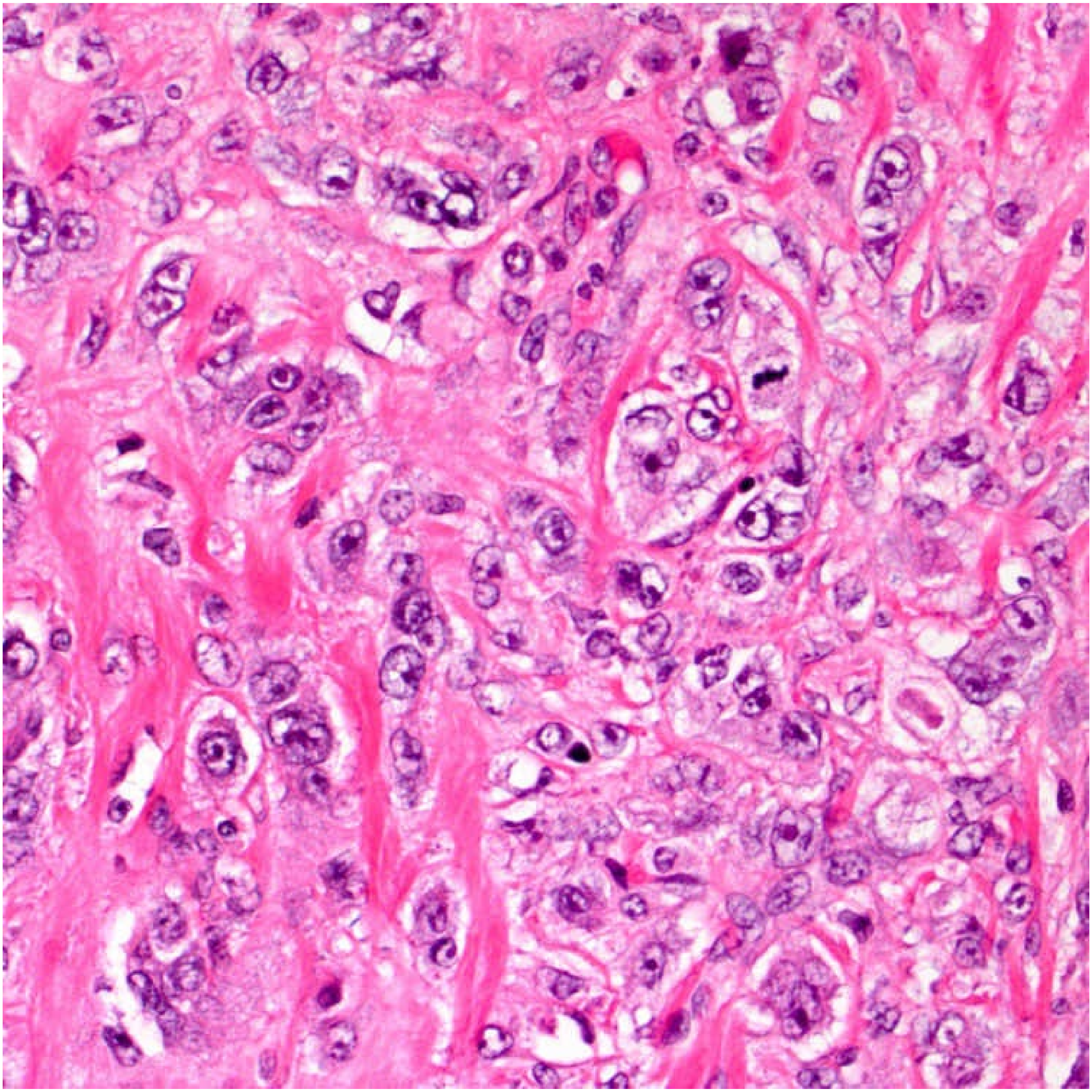
.



Pancreatic Ductal Adenocarcinoma
The cut surface is white, suggesting intense fibrosis. A few little cysts are evident within the mass →. The dilated pancreatic duct is evident ⇨ .



Well-Differentiated Adenocarcinoma
This image shows small to medium-sized glands with haphazard growth embedded in dense desmoplastic stroma. The latter feature is a typical characteristic of this tumor.



Poorly Differentiated Adenocarcinoma
This image shows sheets of poorly differentiated tumor cells as well as single malignant cells. Heterogeneous morphology, encompassing well, moderate, and poor differentiations, is often seen in pancreatic ductal adenocarcinoma.

TERMINOLOGY

Abbreviations

- Pancreatic ductal adenocarcinoma (PDAC)

Synonyms

- Pancreatic adenocarcinoma

- Duct cell adenocarcinoma

Definitions

- Malignant epithelial neoplasm arising in pancreatic ductal system
  - 85-90% of all pancreatic neoplasms
- Predominantly glandular differentiation

ETIOLOGY/PATHOGENESIS

Hereditary Risk Factors

- Family history of pancreatic cancer
- Hereditary pancreatitis
- Peutz-Jeghers syndrome
- Familial atypical multiple mole melanoma syndrome
- *BRCA2* and *BRCA1* mutations

Medical Risk Factors

- Chronic pancreatitis
- Diabetes mellitus
- Previous cholecystectomy or partial gastrectomy

Environmental and Occupational Risk Factors

- Cigarette smoking approximately doubles risk
- Diet high in meat, fat, nitrates, and pork products
- Obesity
- Chemicals (solvents, DDT, gasoline)
- Occupational (coal gas workers, metal working, hide tanning, dry cleaning)

Precursor Lesions

- Pancreatic intraepithelial neoplasia

Molecular Classification

- 4 groups based on genomic analysis
  - Squamous, pancreas progenitor, immunogenic, aberrantly differentiated endocrine exocrine
  - Hold promise for future therapies

CLINICAL ISSUES

Epidemiology

- Age
  - Peak incidence in 7th and 8th decades of life
    - Rare before age 40
    - Majority of cases occur between age 60-80
- Sex
  - M:F = 1.3:1
- Ethnicity
  - More common in Maoris, native Hawaiians, and African Americans

Presentation

- Nonspecific symptoms may delay diagnosis
  - Epigastric pain, weight loss
  - Biliary obstruction, painless jaundice
- Disease associations
  - Trousseau syndrome (migratory thrombophlebitis)
  - Diabetes mellitus
  - Sister Mary Joseph sign (palpable periumbilical nodules)
  - Courvoisier sign (distended, palpable gallbladder)

Treatment

- Resection
  - Only 10-20% of cases resectable at diagnosis
- Chemotherapy before resection, after resection, or both
  - Common regimens: FOLFIRINOX (folate, 5-fluorouracil, irinotecan, oxaliplatin), gemcitabine/nab-paclitaxel
  - Neoadjuvant therapy associated with higher survival

Prognosis

- Dismal; 5-year survival < 5%

IMAGING

General Features

- CT scan commonly used for diagnosis and staging
- MR angiography can help to determine resectability
- Endoscopic US with biopsy reliable for diagnosis and staging
- ERCP/MRCP helps visualize ductal system

MACROSCOPIC

General Features

- Majority in head of pancreas
  - Minority in body/tail, or diffusely involve gland
- Solitary (majority) or multifocal
- Firm, solid, poorly defined, white-yellow mass
  - May have cystic degeneration
- Usually intense fibrotic reaction
  - May make carcinoma difficult to distinguish from background pancreatitis
- Pancreatic duct may be dilated
- May cause stenosis of common bile duct
- Tumors often grossly extend beyond pancreas

MICROSCOPIC

Histologic Features

- Wide differentiation spectrum: Very well to poorly differentiated
  - Glands grow in haphazard fashion and are very infiltrative
- Nuclear features
  - Nuclear crowding and overlapping
  - Nuclei vary in size, shape, and intracellular location in same neoplastic gland
  - Loss of polarity
  - Irregular chromatin distribution
  - Irregular nuclear contour
- Dense desmoplastic stroma
  - Fibroblasts and other inflammatory cells
  - Tumor cells may comprise a small component compared to desmoplastic reaction
- Mucin production
- Some cases have foamy glands
  - Deceptively bland, benign-appearing cells with microvesicular cytoplasm
  - Mimics PanIN, benign glands, or histiocytes
- Some cases composed of large, dilated, invasive glands, often with simple architecture (large duct variant)
  - May simulate (dilated) PanIN
- Perineural, angiolymphatic invasion common
- Tumor may infiltrate larger blood vessels and cause thrombi
- Tumor cells may grow along basement membrane of pancreatic and bile duct (cancerization)
- Associated pancreatitis is common
  - Parenchymal atrophy, fibrosis, islet cell clustering (pseudohyperplasia)

ANCILLARY TESTS

Immunohistochemistry

- Positive for cytokeratins 7, 8, 18, 19
- Positive for CEA, CA19-9, CA125, B72.3

- Positive for MUC1, MUC4, MUC5AC, MUC6
- Positive for claudin-4, fascin, mesothelin, S100 protein
- Loss of nuclear expression of p16 (> 90%) and DPC4/SMAD4 (55%)
- Overexpression of p53 (50-75%)

Histologic Patterns and Variants

- Colloid carcinoma
  - Neoplastic epithelial cells suspended in large pools of extracellular mucin
  - Colloid component must comprise at least 80% of tumor
  - Almost always arises in association with intestinal-type IPMN
  - Positive for CDX2 and MUC2
- Signet ring cell carcinoma
  - Signet ring cells comprise > 50% of tumor
  - Extremely poor prognosis
  - Metastasis from stomach, breast, and colon should be excluded
- Adenosquamous carcinoma
  - Squamous differentiation in at least 30% of tumor
  - Poorer outcome compared to PDAC
- Carcinomas with mixed differentiation: By definition, each component should comprise at least 30% of tumor
  - Mixed ductal-neuroendocrine carcinoma
  - Mixed acinar-ductal carcinoma
  - Mixed acinar-ductal-neuroendocrine carcinoma
- Medullary carcinoma
  - Poorly differentiated carcinoma with pushing rather than infiltrating borders
  - Some cases have prominent tumor-infiltrating lymphocytes
  - Associated with microsatellite instability, Lynch syndrome, EBV
  - Better prognosis than conventional ductal adenocarcinoma
- Undifferentiated carcinoma ± osteoclastic-like giant cells
  - Majority of tumor cells do not show any specific differentiation
  - Poorly cohesive, stroma is usually scant
  - Extremely poor prognosis
  - Several histologic variants (WHO 2010)
    - Anaplastic giant cell variant: Pleomorphic tumor cells mixed with bizarre multinucleated tumor giant cells
    - Sarcomatoid carcinoma variant: Composed of malignant spindle cells
    - Carcinosarcoma variant: Adenocarcinoma mixed with sarcomatoid spindle cell elements
    - Undifferentiated carcinoma with osteoclast-like giant cells: Pleomorphic spindle cells mixed with nonneoplastic, osteoclast-like giant cells
      - Giant cells often have > 20 nuclei and are found around necrosis and hemorrhage
      - Often associated with PanIN, PDAC, or mucinous cystic neoplasm
- Hepatoid carcinoma
  - Significant component demonstrates hepatocellular differentiation
  - Hepatocellular markers (arginase-1, Hep-Par1) positive

- Can occur in association with ductal adenocarcinoma, acinar cell carcinoma, or neuroendocrine carcinoma
  - Metastasis from liver primary should be excluded
- Clear cell carcinoma
  - Clear cytoplasm resembles renal cell carcinoma
  - Common focal finding in PDAC
- Uncommon tumors of probable ductal phenotype
  - Oncocytic carcinoma, nonmucinous carcinoma, glycogen-poor cystadenocarcinoma, choriocarcinoma, ciliated cell adenocarcinoma, microadenocarcinoma

DIFFERENTIAL DIAGNOSIS

Chronic Pancreatitis

- Often involves younger patients (< 40 years)
- Diffuse scarring of gland without discrete mass
- Relatively preserved lobular architecture

Normal/Reactive Duct Changes

- Very well-differentiated tumors mimic normal or reactive ducts; these features favor PDAC
  - Small glands adjacent to muscular arteries without intervening stroma or acini
  - Incomplete gland formation
  - Disorganized, haphazard growth of neoplastic glands
  - 4x variation in nuclear size within same gland

Ampullary/Periampullary Carcinomas

- Epicenter of mass (gross) and precursor lesions differentiates from PDAC
- Strong diffuse staining for CK20, CDX2 favors intestinal origin

Acinic Cell Carcinoma

- Highly cellular with acinar, trabecular, &/or solid patterns
- Eosinophilic granular cytoplasm
- Basally located nuclei with single prominent nucleolus
- Positive for trypsin and chymotrypsin
- Negative for CK7

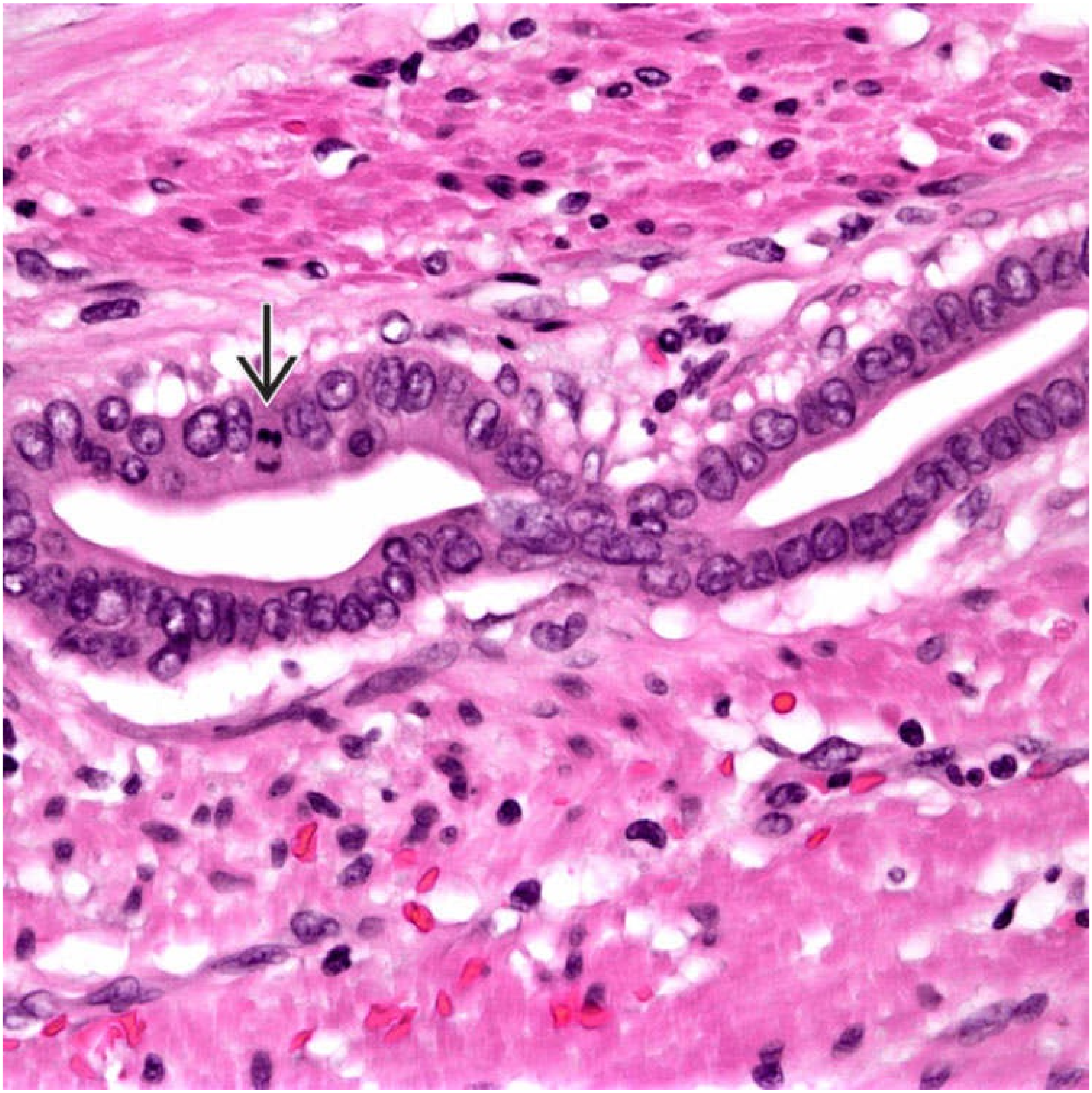
Neuroendocrine Neoplasms

- Nesting/trabecular pattern, hyalinized stroma
- Uniform nuclei, “salt and pepper” chromatin (low-grade NET)
- Positive for chromogranin, synaptophysin

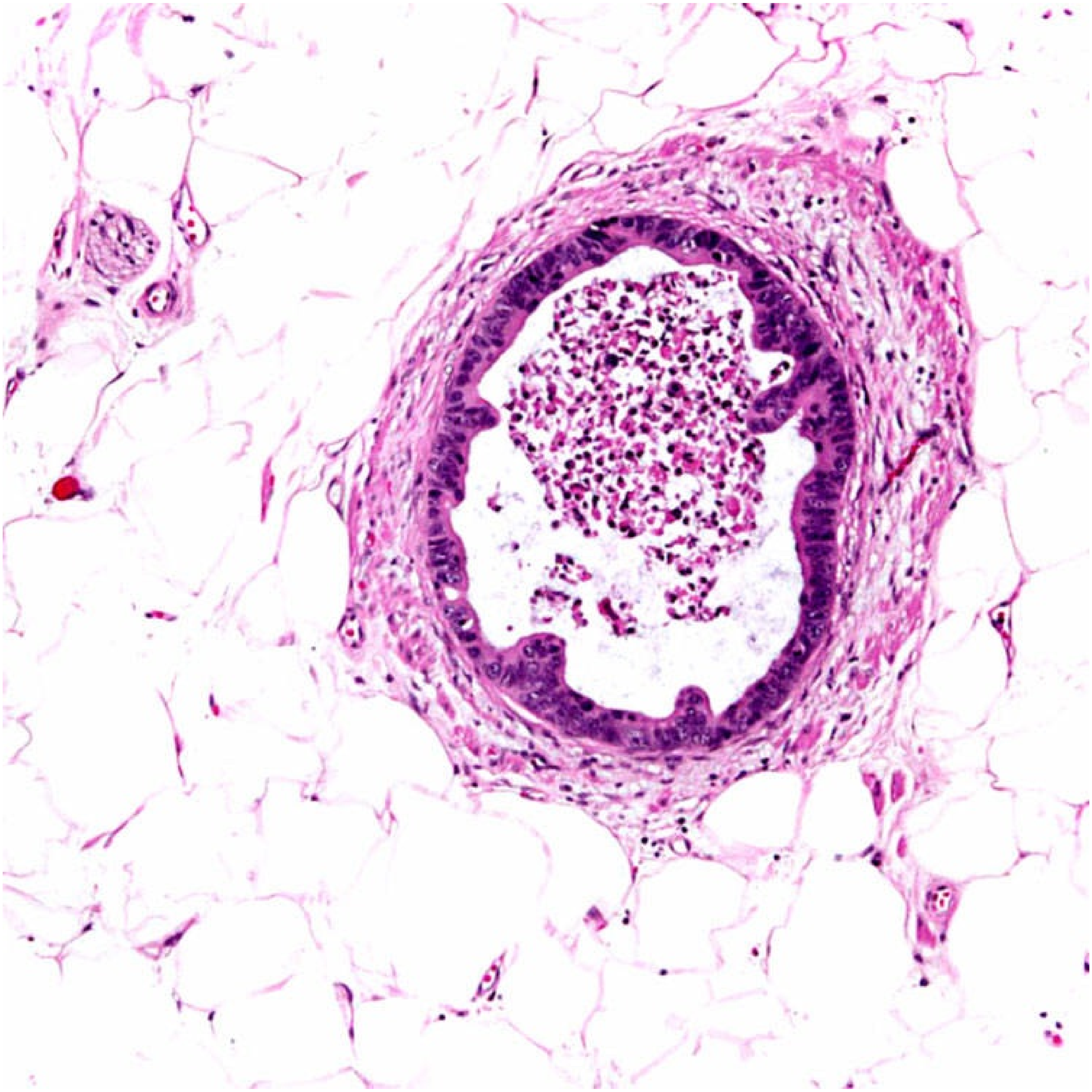
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Perineural or angiolymphatic invasion in retroperitoneal soft tissue margin is underrecognized basis for surgical failure
  - > 1/2 of patients have extrapancreatic nerve involvement in this area
- Lymph node metastases present at time of surgery in 70-80% of patients

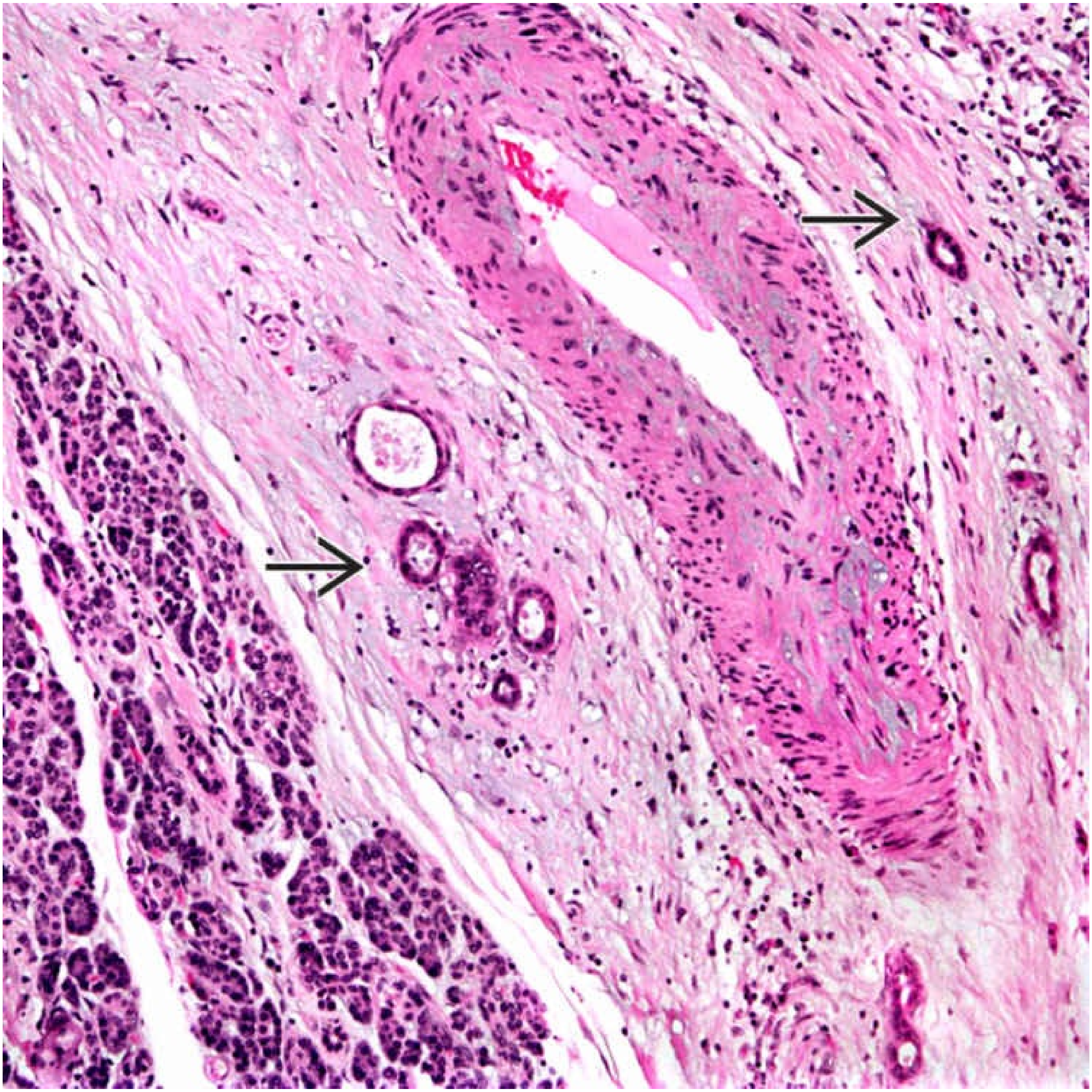


Cytologic Features
Cytologic clues to the diagnosis of well-differentiated cases include variation in nuclear size, haphazard arrangement of nuclei, irregular nuclear membranes, and mitoses →.



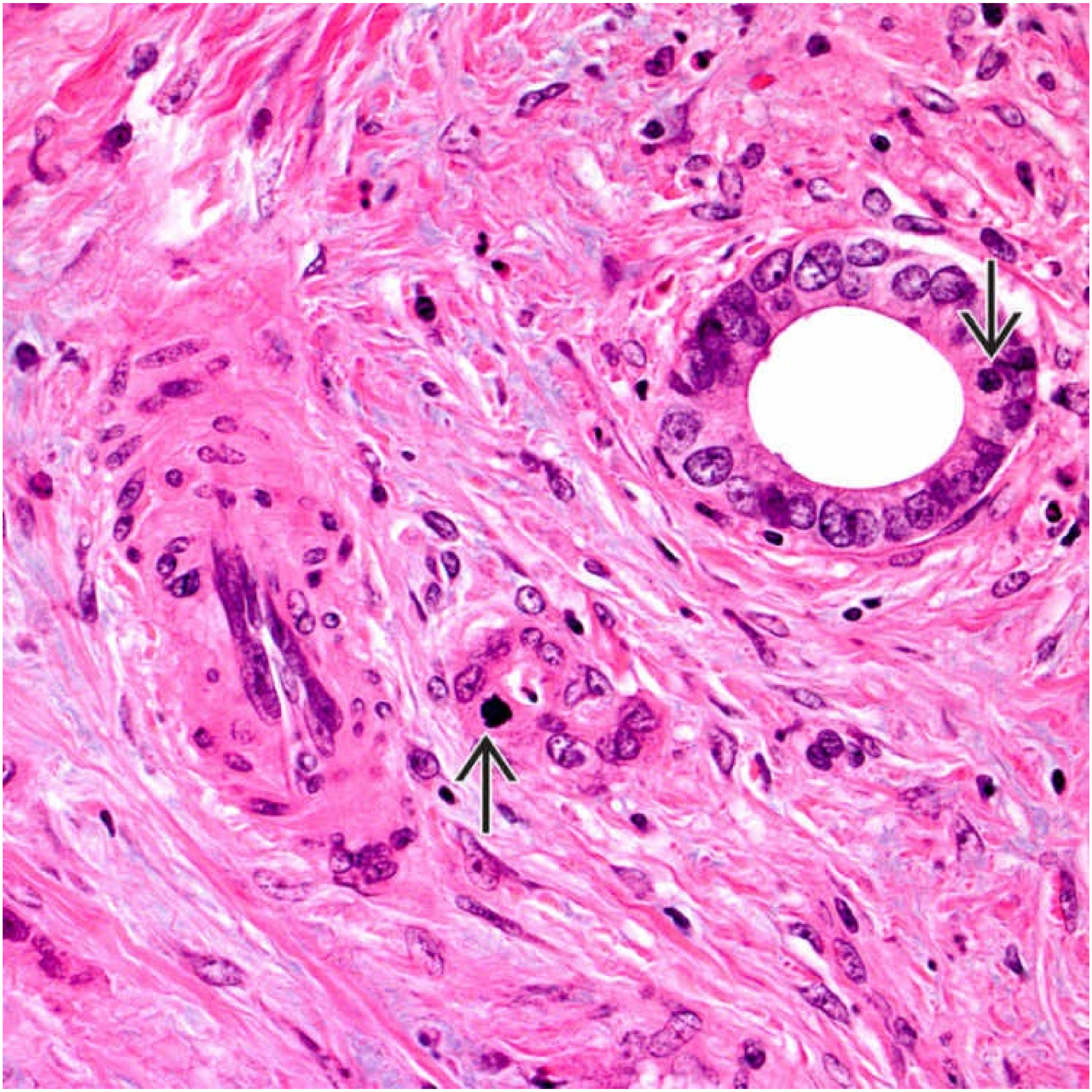
Isolated Malignant Gland in Fat

A well-differentiated malignant gland is present in the peripancreatic fat. This can be a useful clue to establish the diagnosis.



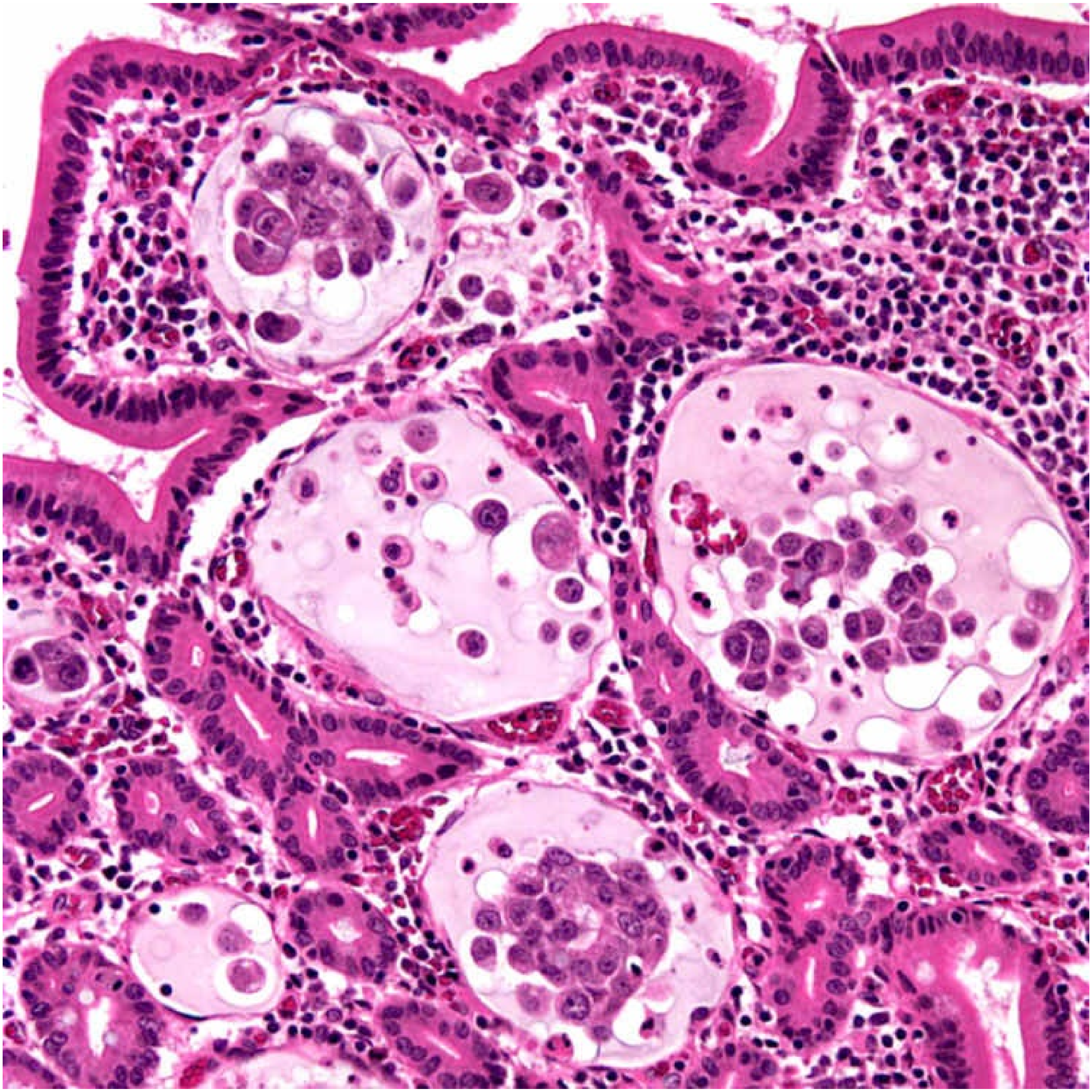
Malignant Glands Adjacent to Large Artery

Small infiltrating malignant glands → are shown directly adjacent to a muscular artery without intervening acinar parenchyma. This finding does not occur in benign pancreas and is a characteristic feature of malignancy.

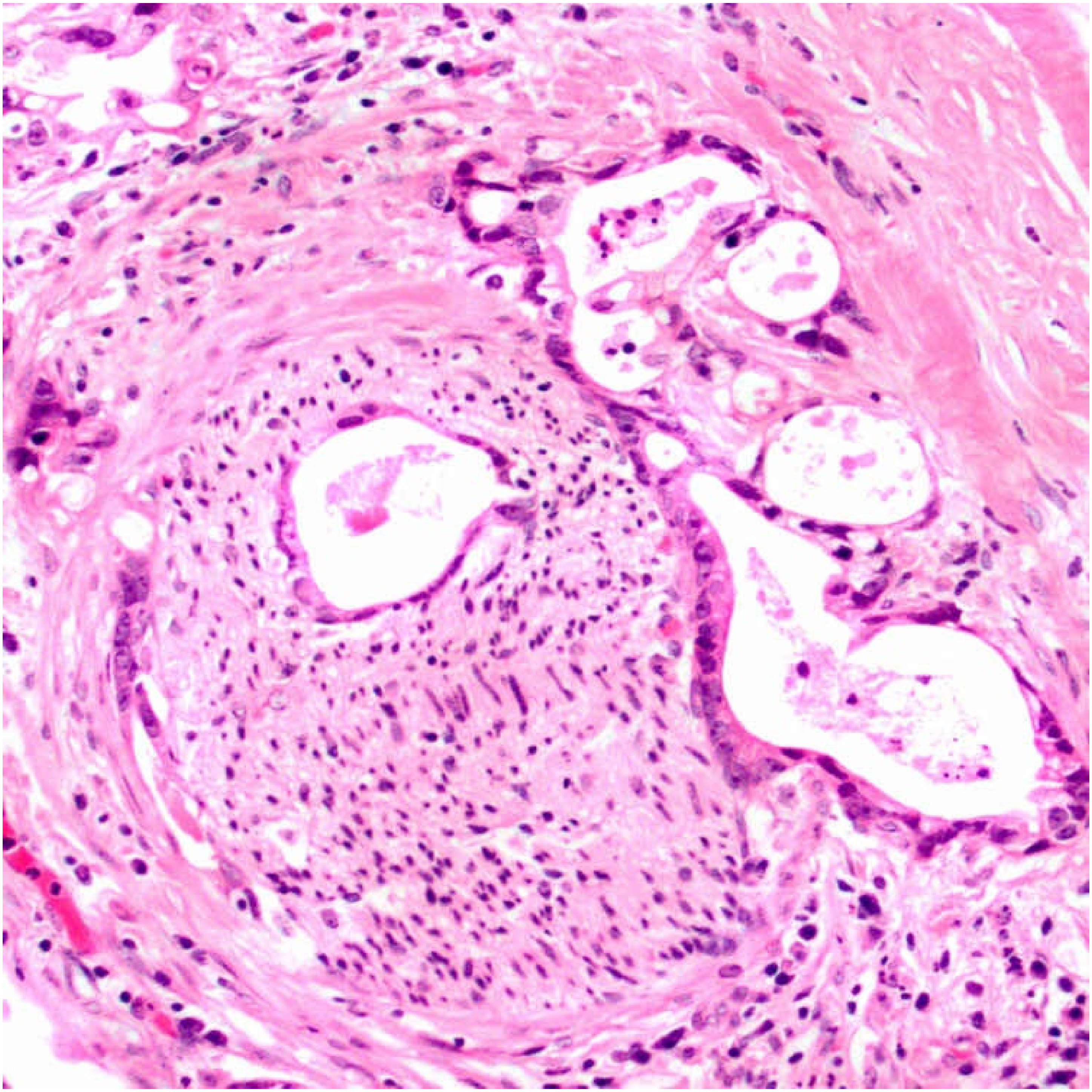


Malignant Glands Adjacent to Artery

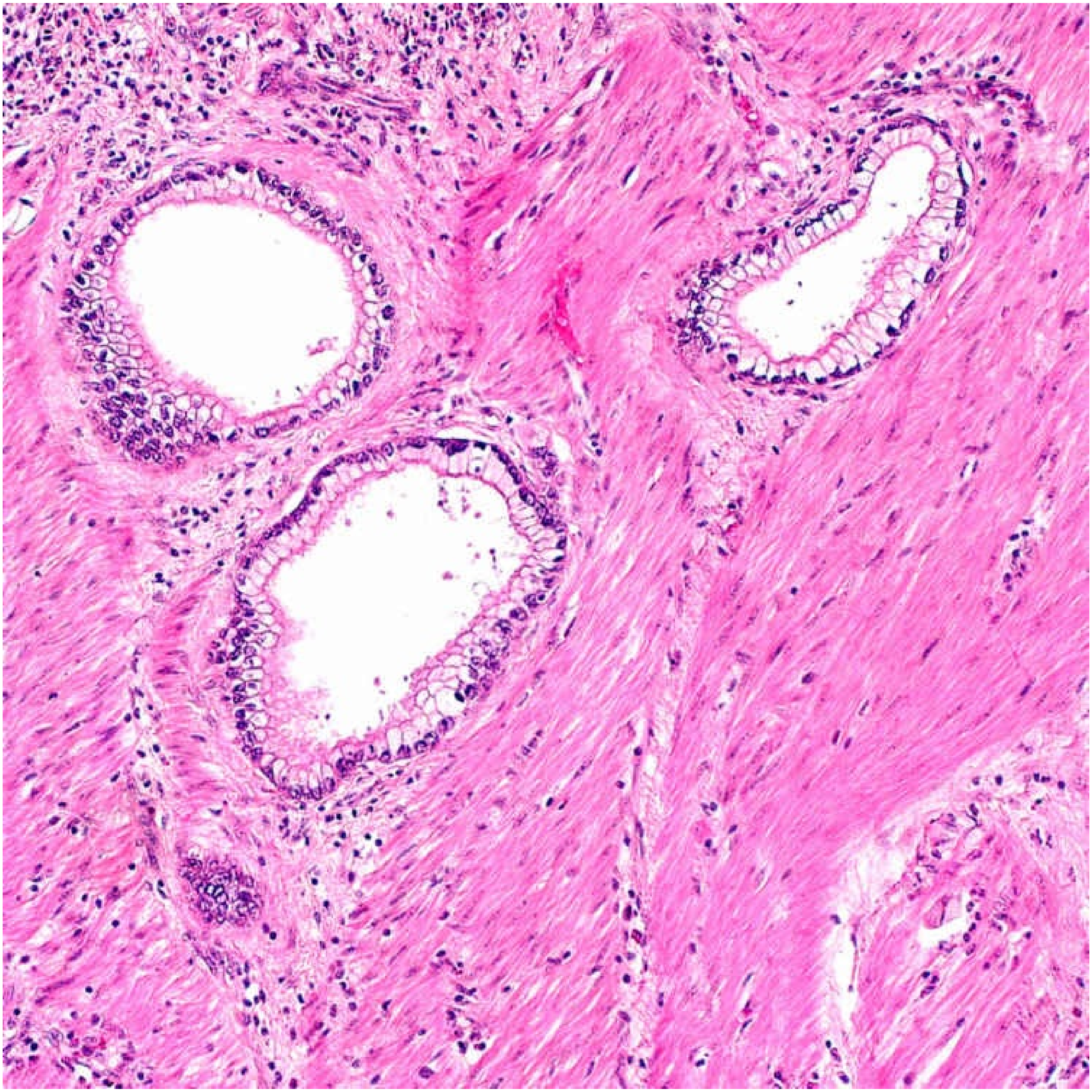
Glands directly adjacent to a muscular artery are a clue to malignancy. Note the prominent mitoses → and irregular nuclear membranes in these neoplastic glands as well.



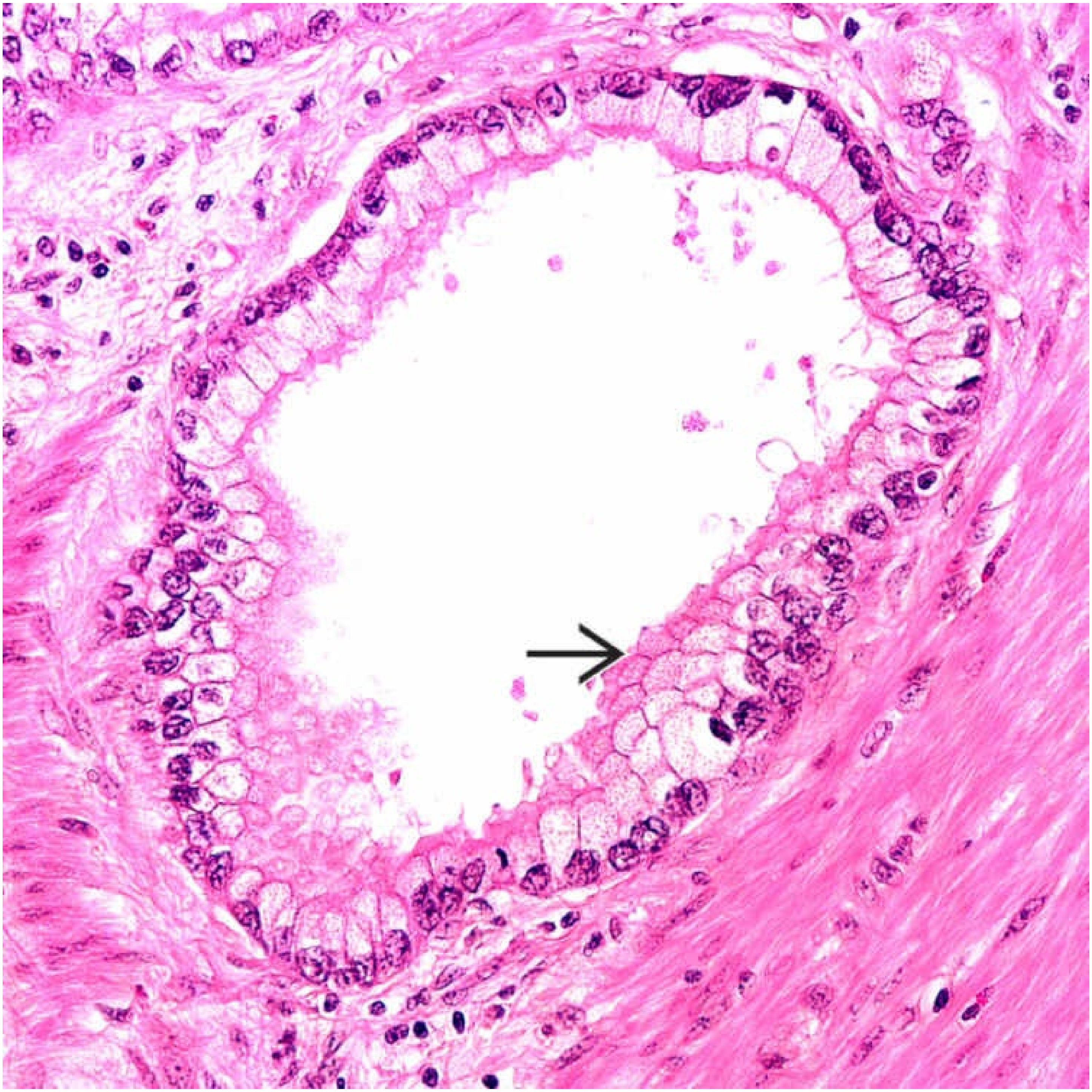
Lymphatic Invasion
This image shows extensive involvement of the duodenal lymphovascular spaces.



Perineural Invasion
Perineural invasion is a common feature of pancreatic ductal adenocarcinoma.

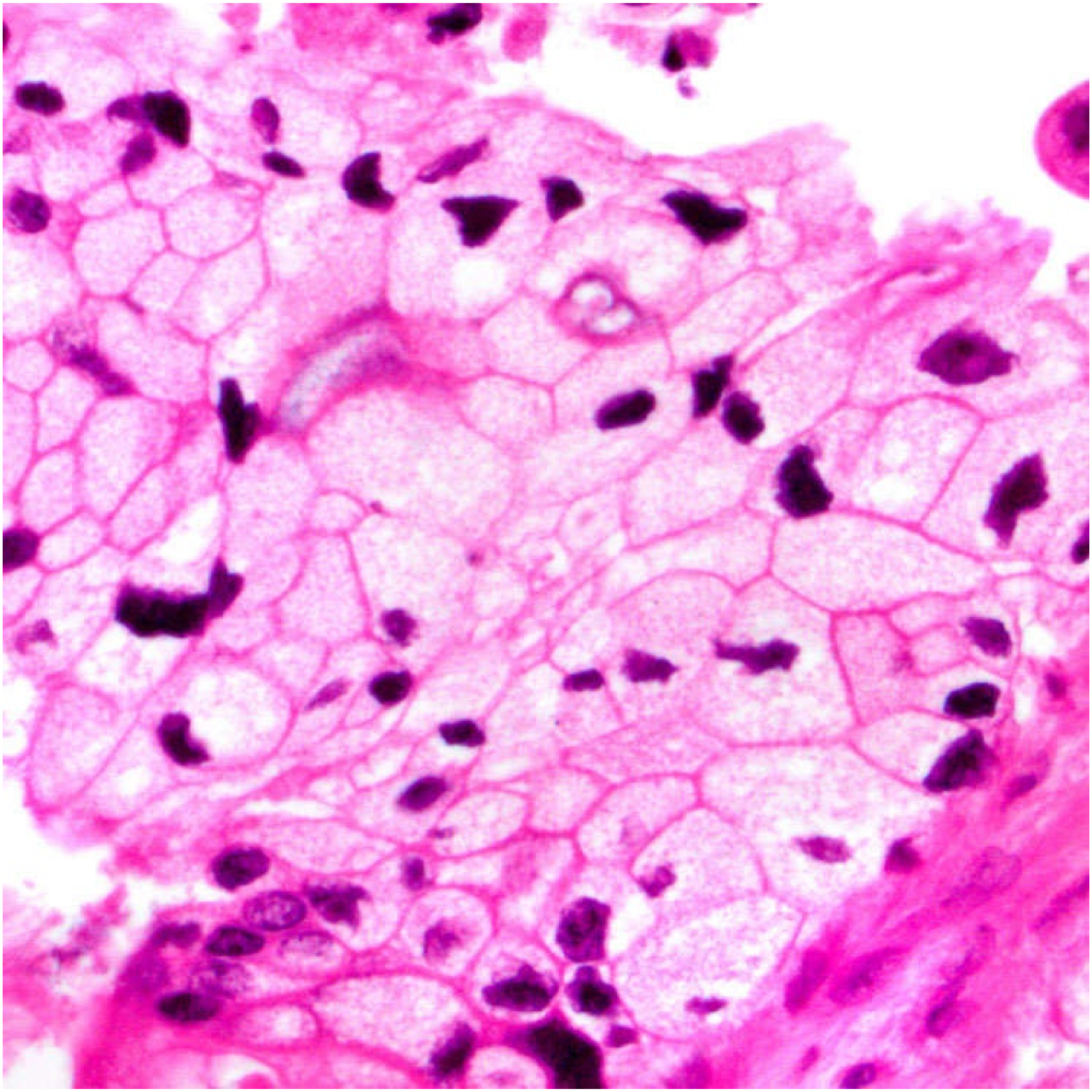


Foamy Gland Pattern
This image shows well-formed glands with clear foamy cytoplasm infiltrating the muscularis propria of the duodenum.

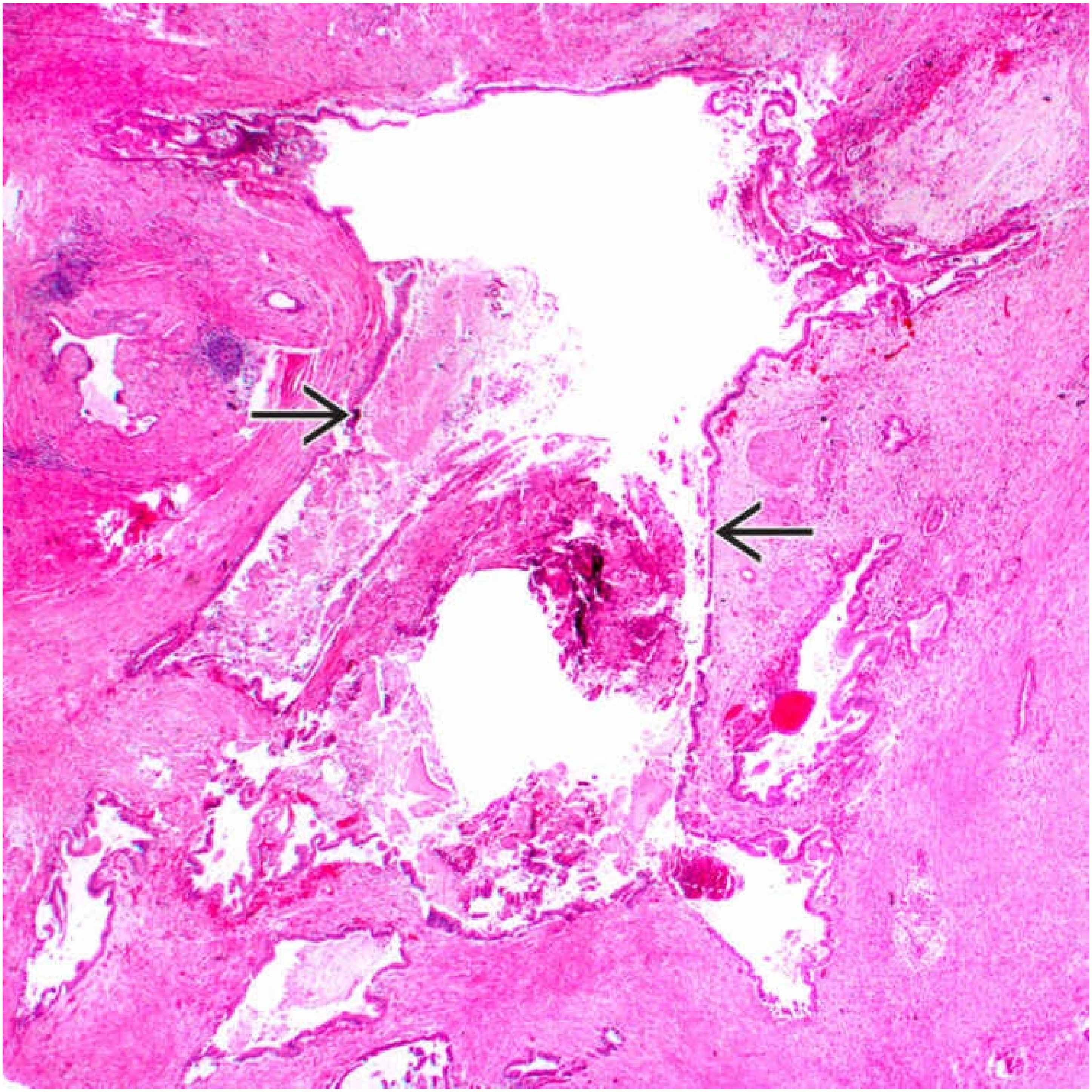


Foamy Gland Pattern

This image shows basally located round nuclei, microvesicular cytoplasm, and distinctive cytoplasmic condensation (brush border-like zone) →. The cytology is deceptively bland and mimics pancreatic intraepithelial neoplasm (PanIN) 1A.

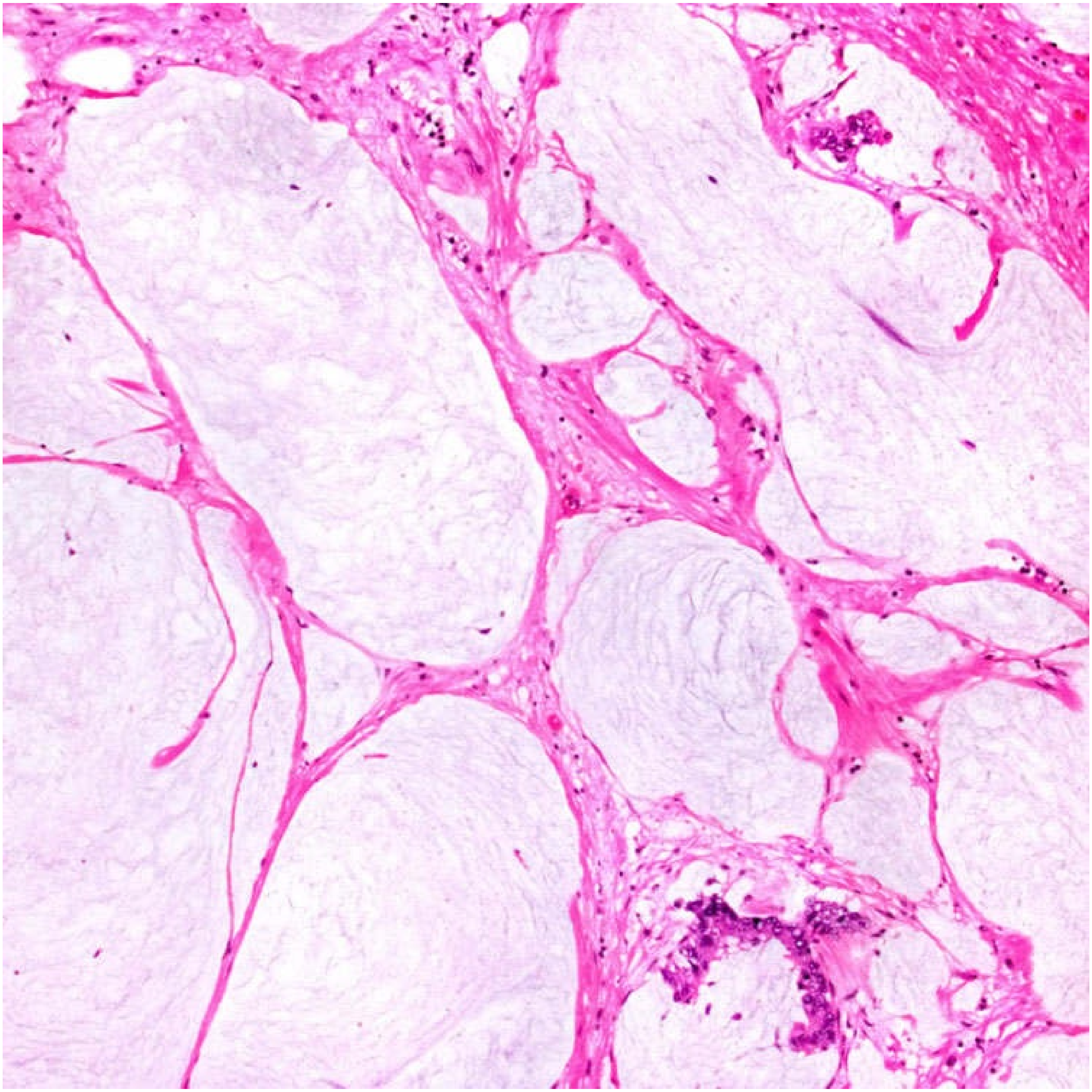


Foamy Gland Pattern
This image shows tumor cells with microvesicular cytoplasm, raisinoid nuclei, and low nuclear:cytoplasmic ratio, mimicking a collection of foamy histiocytes.



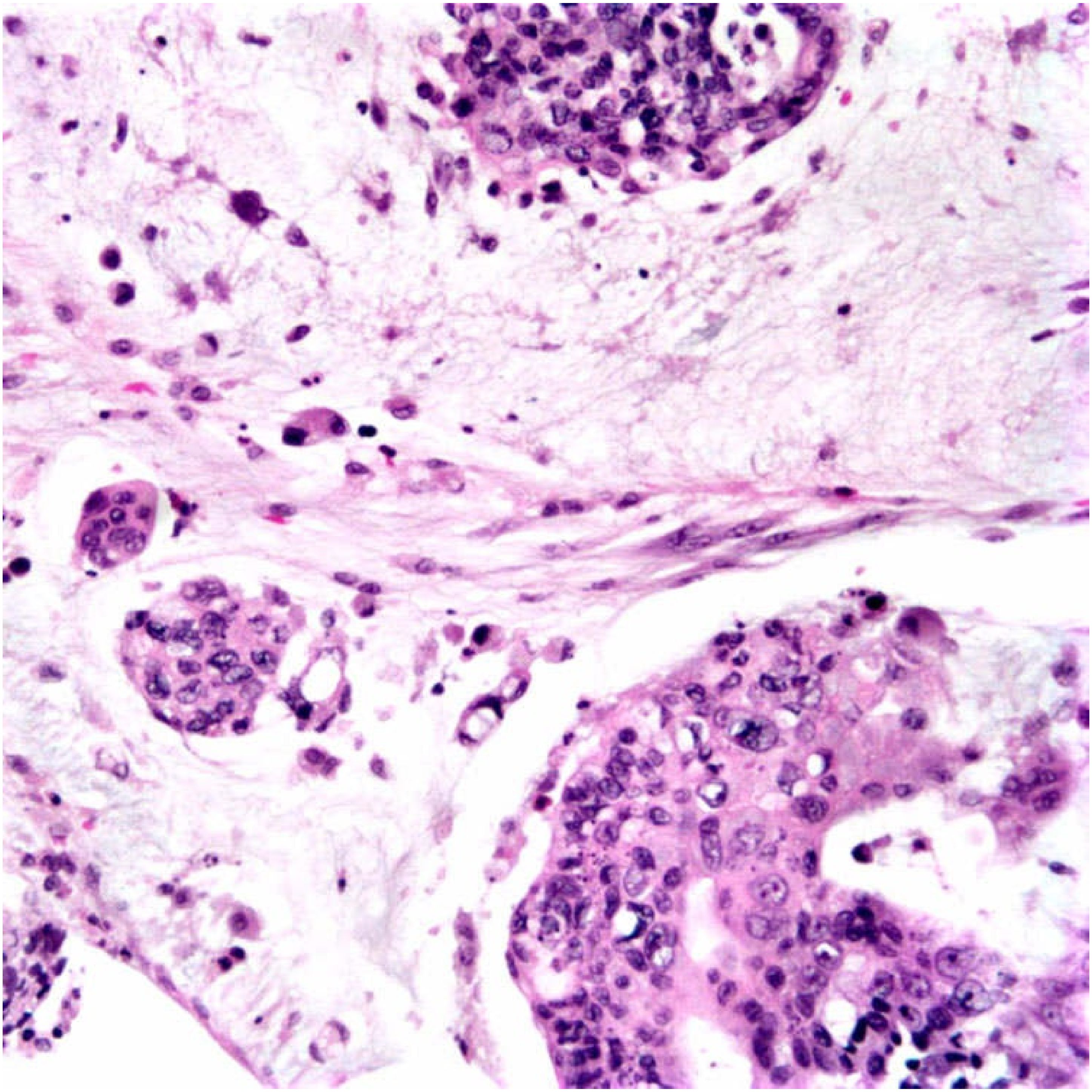
Large Duct Pattern

This image shows cystically dilated neoplastic ducts → that can mimic PanIN or branch-duct IPMN. It can be differentiated from the latter based on the absence of low-grade epithelium in the duct lining.



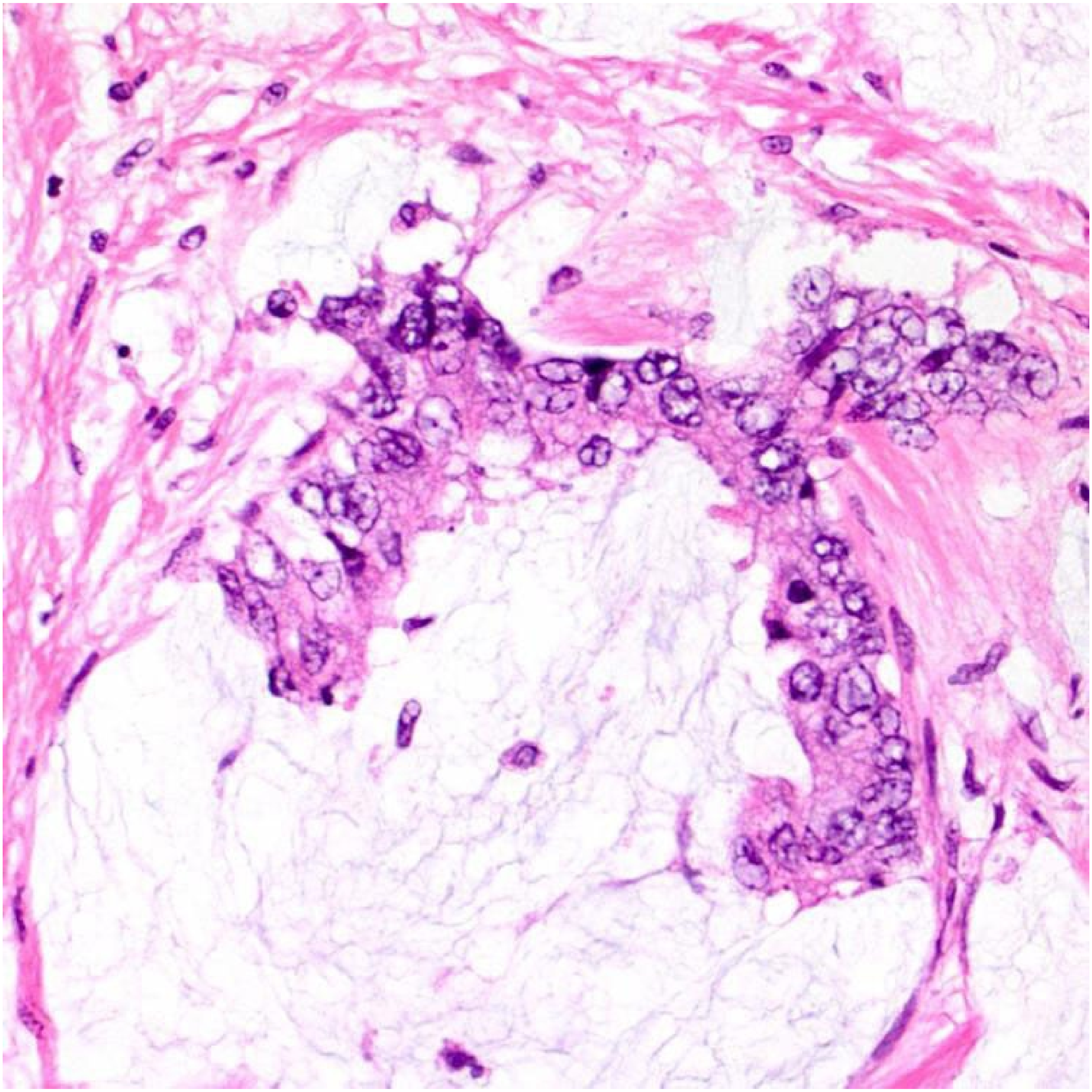
Colloid Variant

The mucinous or colloid pattern of pancreatic adenocarcinoma features neoplastic epithelium that is suspended in, or partially lines, large pools of extracellular mucin.

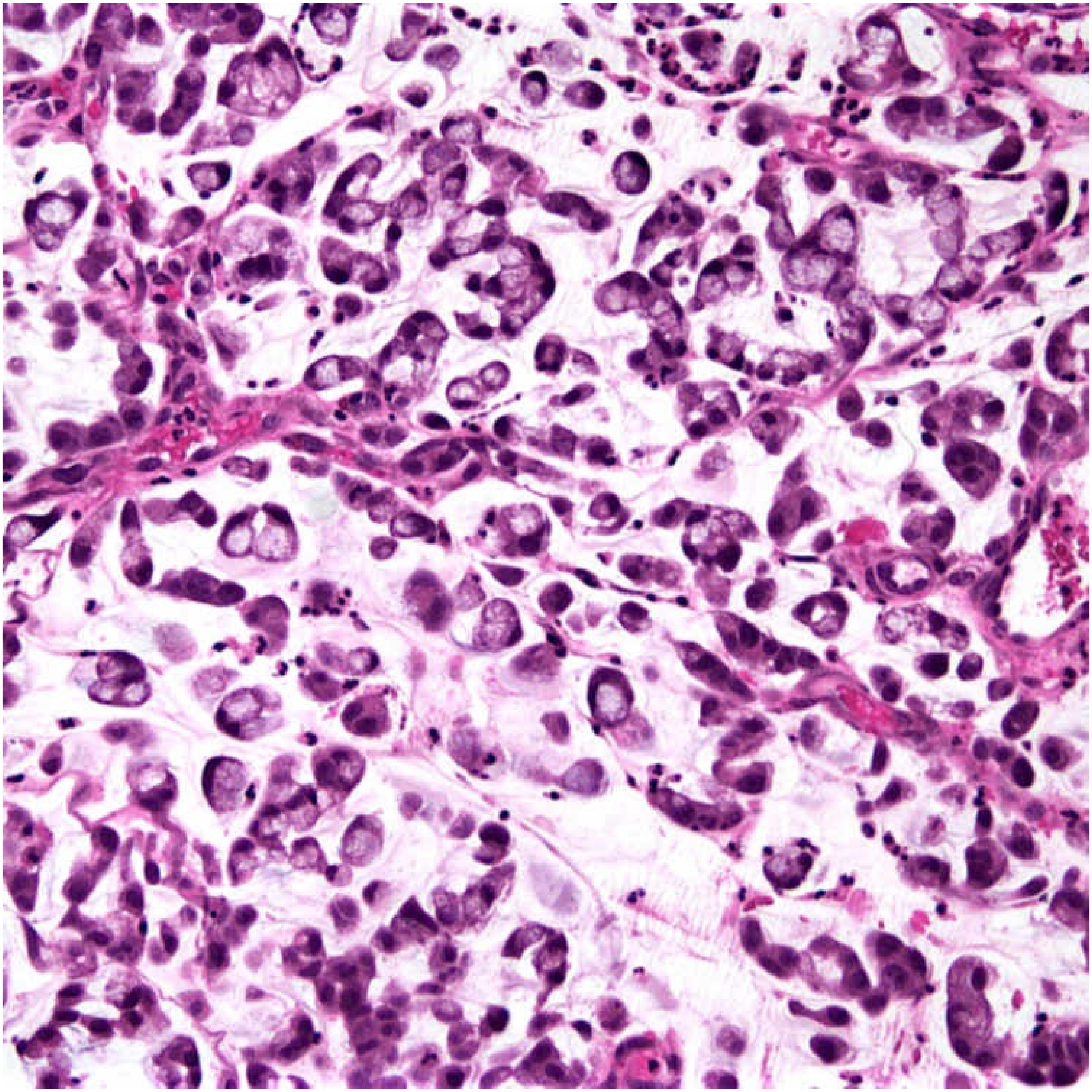


Colloid Variant

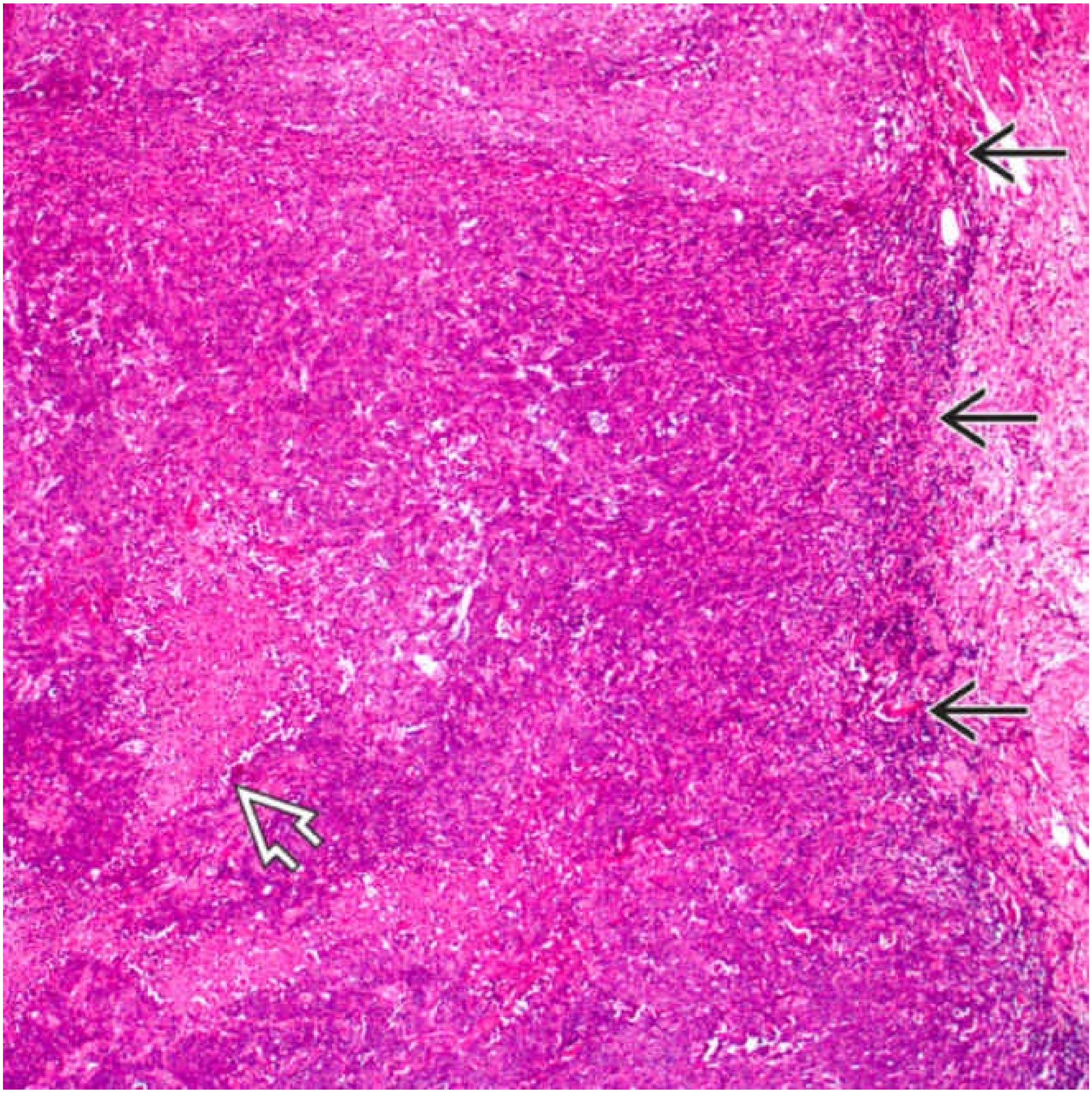
This image shows detached clusters of malignant cells floating in pools of mucin. Colloid carcinomas are almost always associated with intestinal-type intraductal papillary mucinous neoplasm.



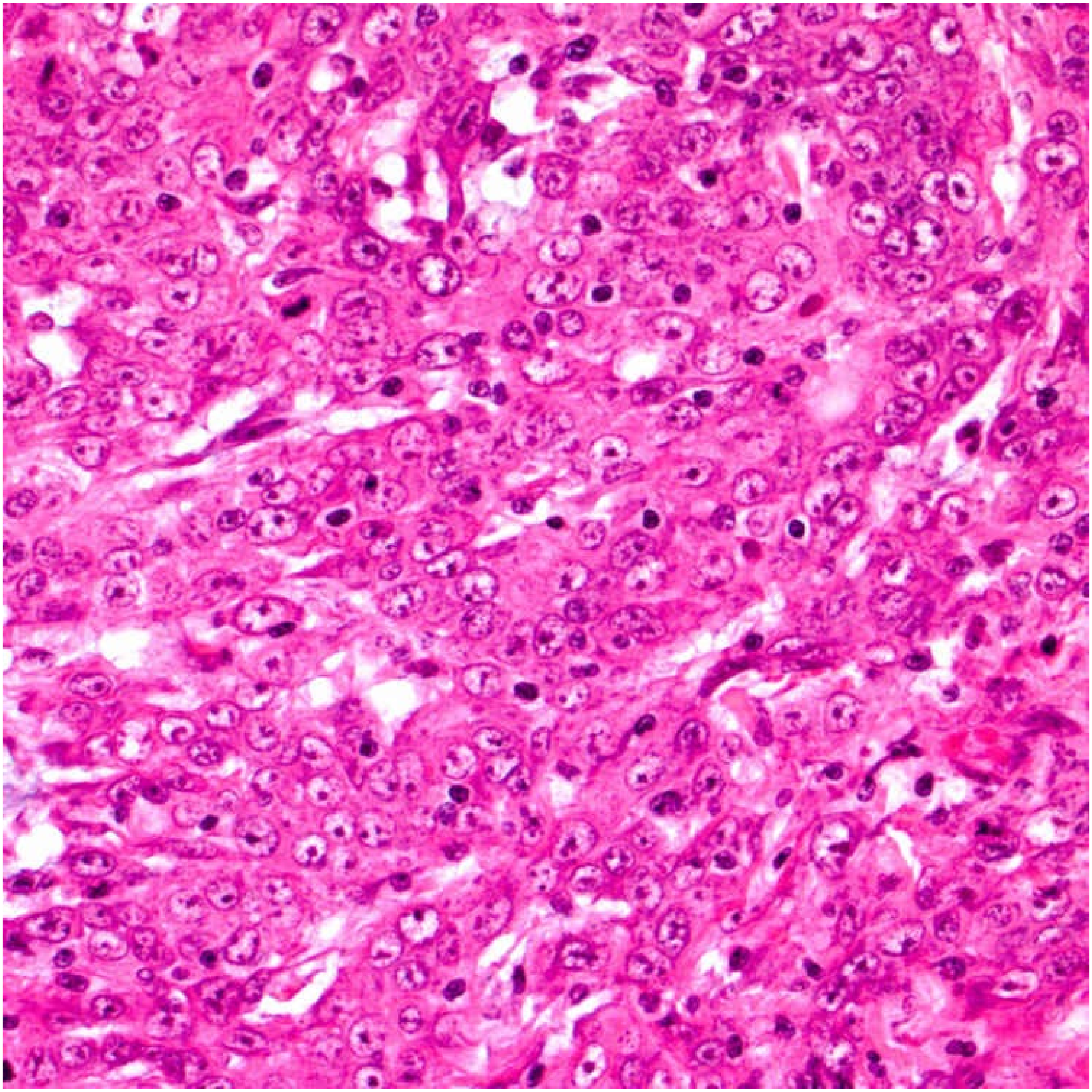
Colloid Variant
High-power magnification demonstrates atypical cytology of the lining epithelium.



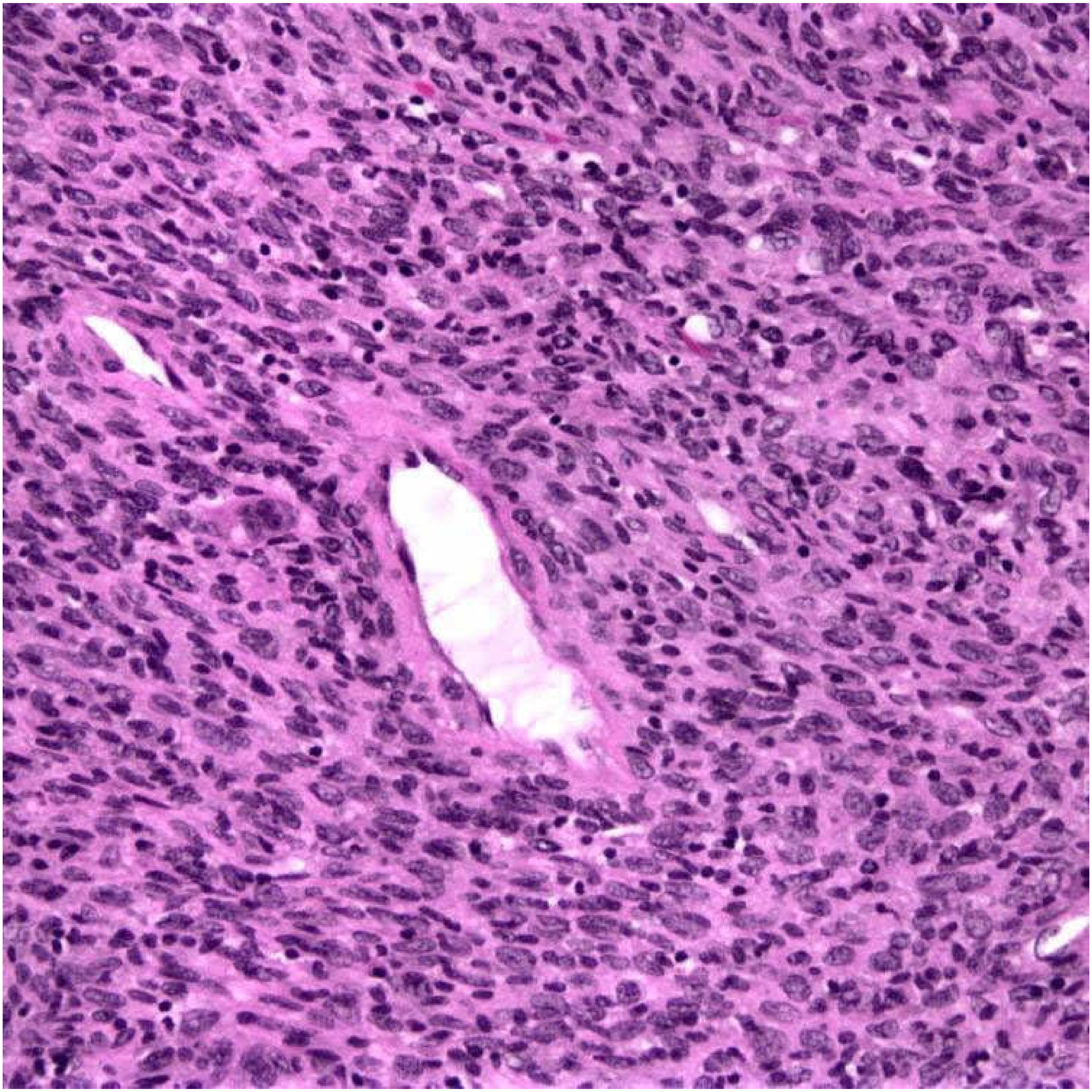
Pancreatic Ductal Adenocarcinoma, Signet Ring Cell Variant
Most tumor cells have signet ring cell morphology. This is an aggressive variant of adenocarcinoma.



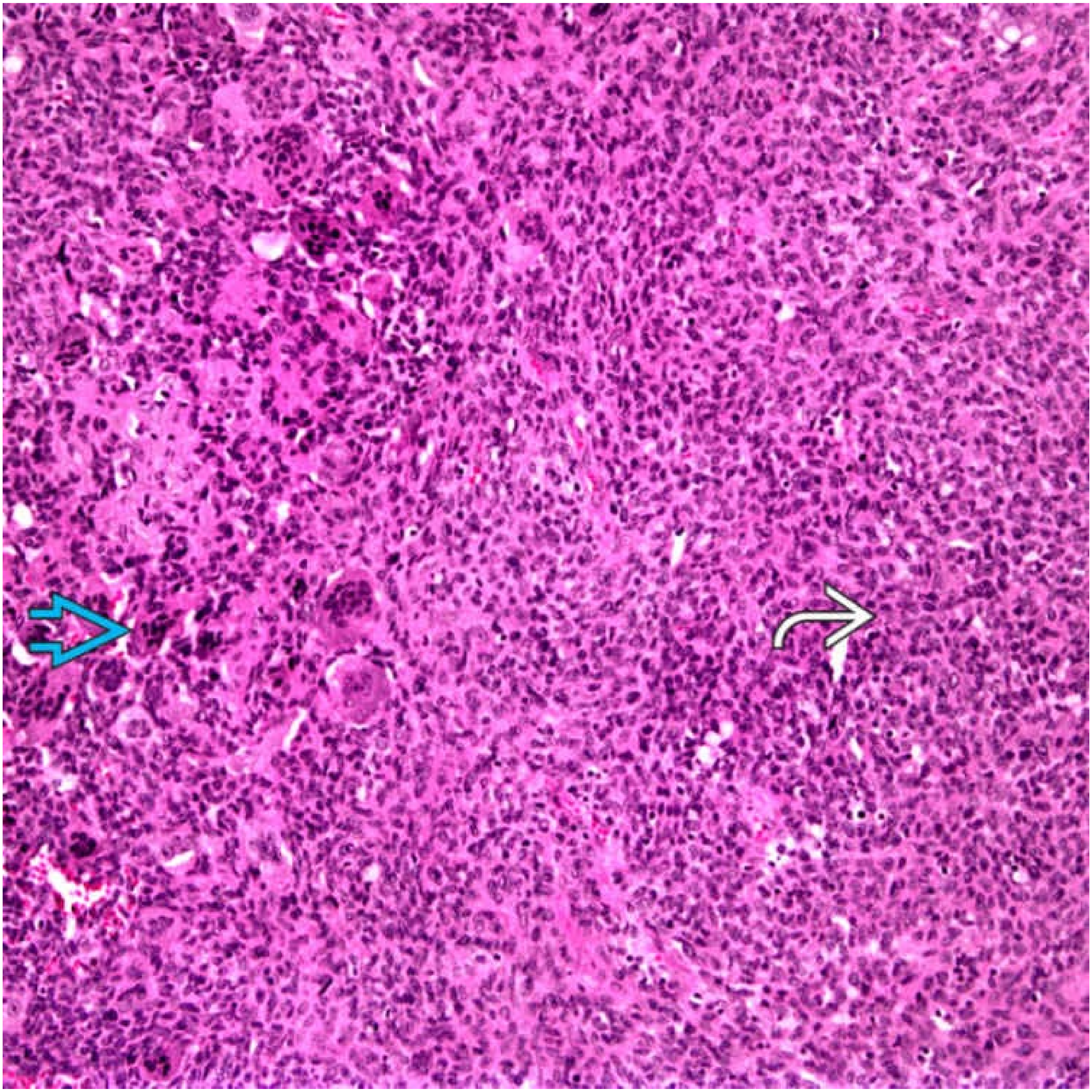
Medullary Variant
This image shows well-defined borders → and foci of necrosis ⇨ .



Medullary Variant
This image shows syncytial growth pattern containing poorly differentiated cells with scattered tumor-infiltrating lymphocytes. This variant is associated with Lynch syndrome, microsatellite instability, and has a better prognosis.



Undifferentiated Carcinoma, Sarcomatoid Carcinoma Variant
Malignant spindle cells with moderate atypia are seen resembling a spindle cell sarcoma. A component of typical adenocarcinoma can be present (carcinosarcoma).



Undifferentiated Carcinoma With Osteoclast-Like Giant Cells
This image shows multinucleated, nonneoplastic, osteoclast-like giant cells and a poorly differentiated, spindle cell neoplastic component. These giant cells often have > 20 nuclei and cluster around areas of hemorrhage or necrosis.

SELECTED REFERENCES

1. Bailey, P, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. *Nature*. 2016; 531(7592):47–52.
2. Hidalgo, M, et al. Addressing the challenges of pancreatic cancer: Future directions for improving outcomes. *Pancreatology*. 2014. [ePub].
5. Hruban, RH, et al. Pancreatic adenocarcinoma: update on the surgical pathology of carcinomas of ductal origin and PanINs. *Mod Pathol*. 2007; 20(Suppl 1):S61–S70.

6. Adsay, NV, et al. Ductal neoplasia of the pancreas: nosologic, clinicopathologic, and biologic aspects. *Semin Radiat Oncol*. 2005; 15(4):254–264.

3. Shi, C, et al. Familial pancreatic cancer. *Arch Pathol Lab Med*. 2009; 133(3):365–374.
4. Stessin, AM, et al. Neoadjuvant radiation is associated with improved survival in patients with resectable pancreatic cancer: an analysis of data from the surveillance, epidemiology, and end results (SEER) registry. *Int J Radiat Oncol Biol Phys*. 2008; 72(4):1128–1133.
7. Fesinmeyer, MD, et al. Differences in survival by histologic type of pancreatic cancer. *Cancer Epidemiol Biomarkers Prev*. 2005; 14(7):1766–1773.
8. Forrester, DW, et al. Carcinoma of the pancreas: a review of 342 cases. *J R Coll Surg Edinb*. 1980; 25(6):436–443.
9. Cubilla, AL, et al. Classification of pancreatic cancer (nonendocrine). *Mayo Clin Proc*. 1979; 54(7):449–458.
10. Cubilla, A, et al. Pancreas cancer. I. Duct adenocarcinoma. A clinical-pathologic study of 380 patients. *Pathol Annu*. 1978; 13(Pt 1):241–289.
11. Kissane, JM. Carcinoma of the exocrine pancreas: pathologic aspects. *J Surg Oncol*. 1975; 7(2):167–174.

Undifferentiated Carcinoma

KEY FACTS

Terminology

- Malignant epithelial neoplasm with significant component showing no definite differentiation
  - Wide range of morphologic findings ranging from pleomorphic epithelioid cells to multinucleated giant cells to spindle cells

Clinical Issues

- Rare
- Prognosis is dismal, often < 1 year
- Surgical resection is treatment of choice

Macroscopic

- Large, fleshy mass, often with hemorrhage and necrosis, that invades adjacent organs
- Presentation as cystic mass has been reported

Microscopic

- Heterogeneous features consisting of anaplastic, giant cell and spindle cell components in varying proportions
- Variably present large, benign-appearing, multinucleated osteoclast-like giant cells

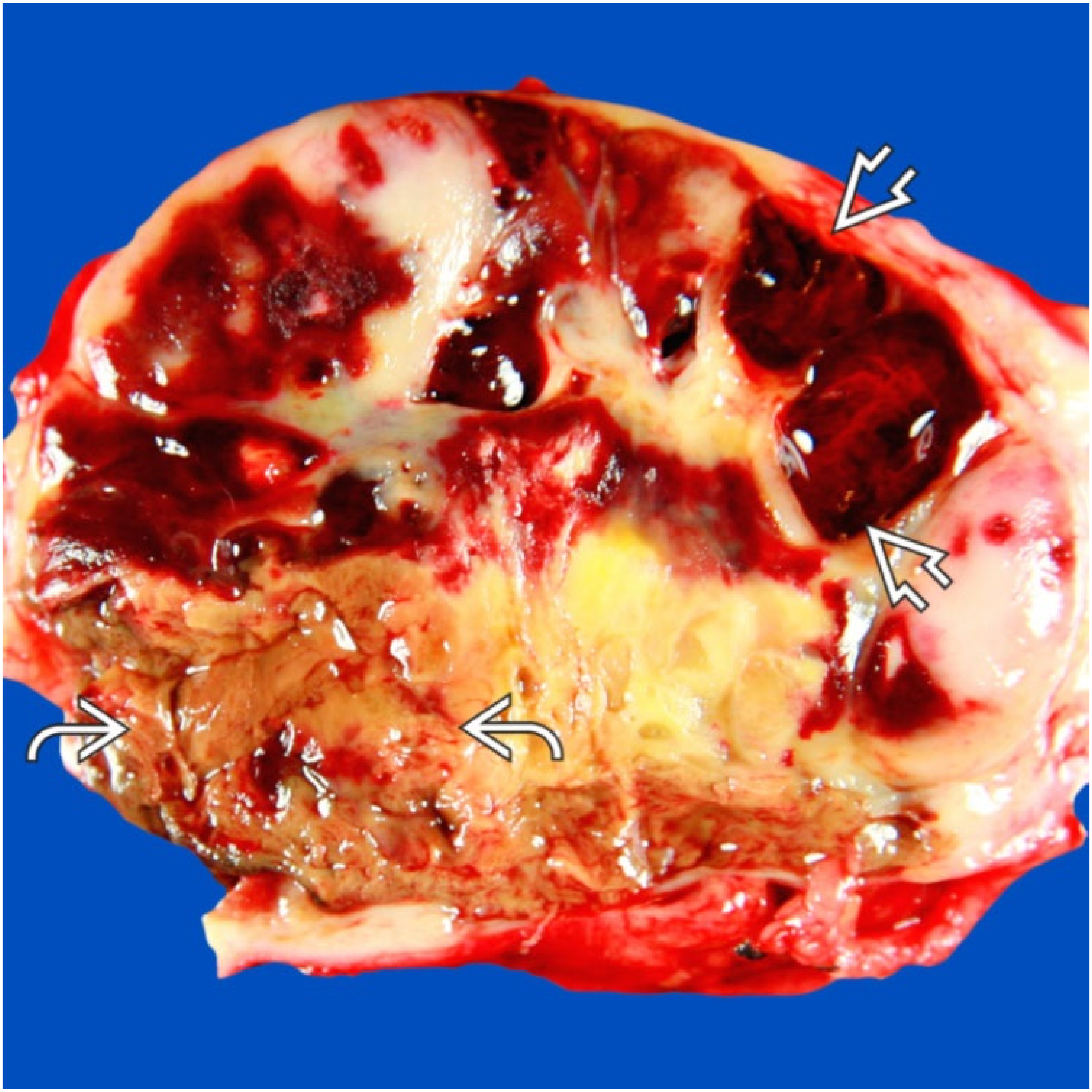
Ancillary Tests

- CK7, CK8, CK18, and CK19 can be positive but usually focal
- Neoplastic spindle cells may express smooth muscle actin but not desmin

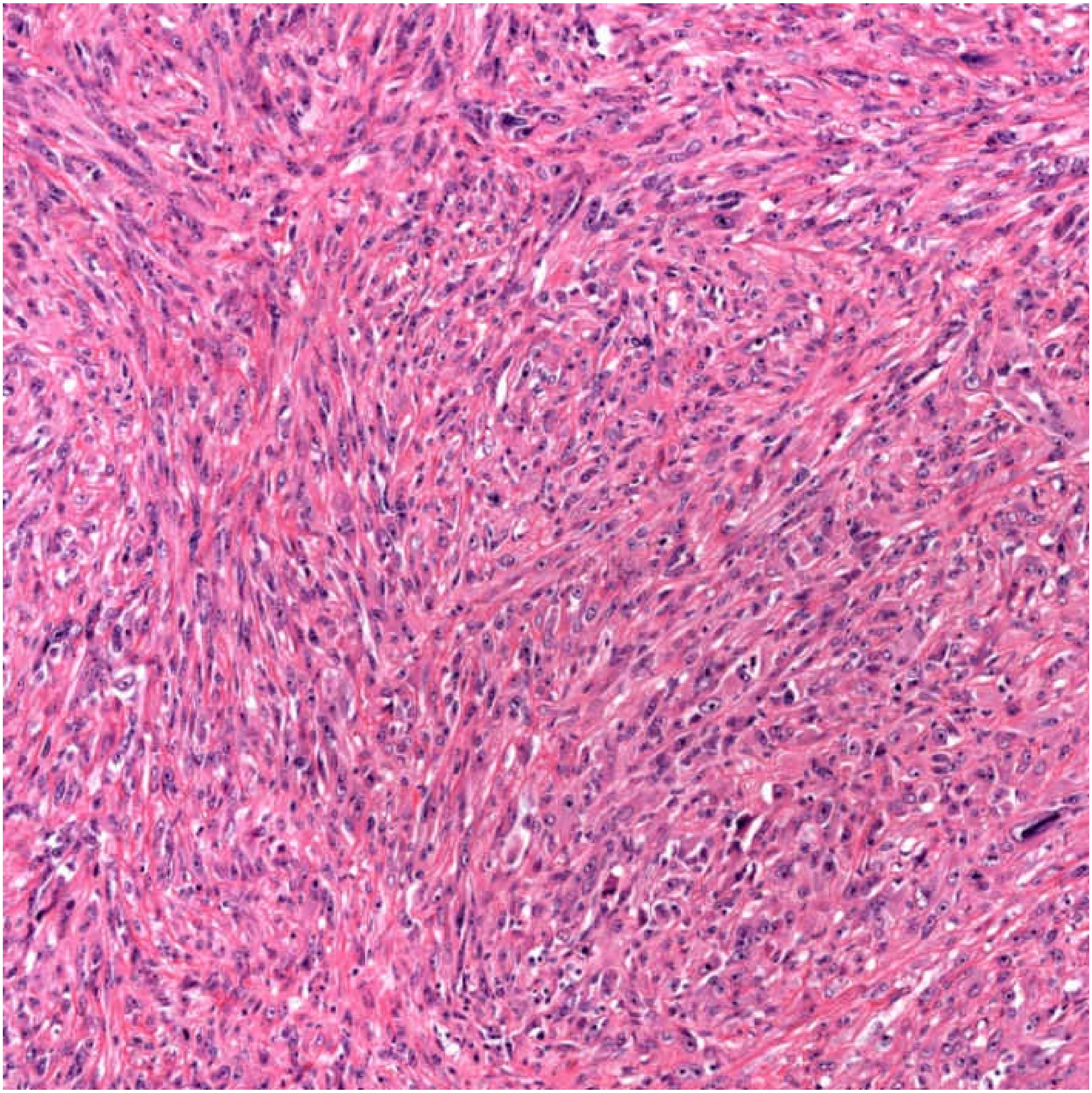
Top Differential Diagnoses

- Melanoma

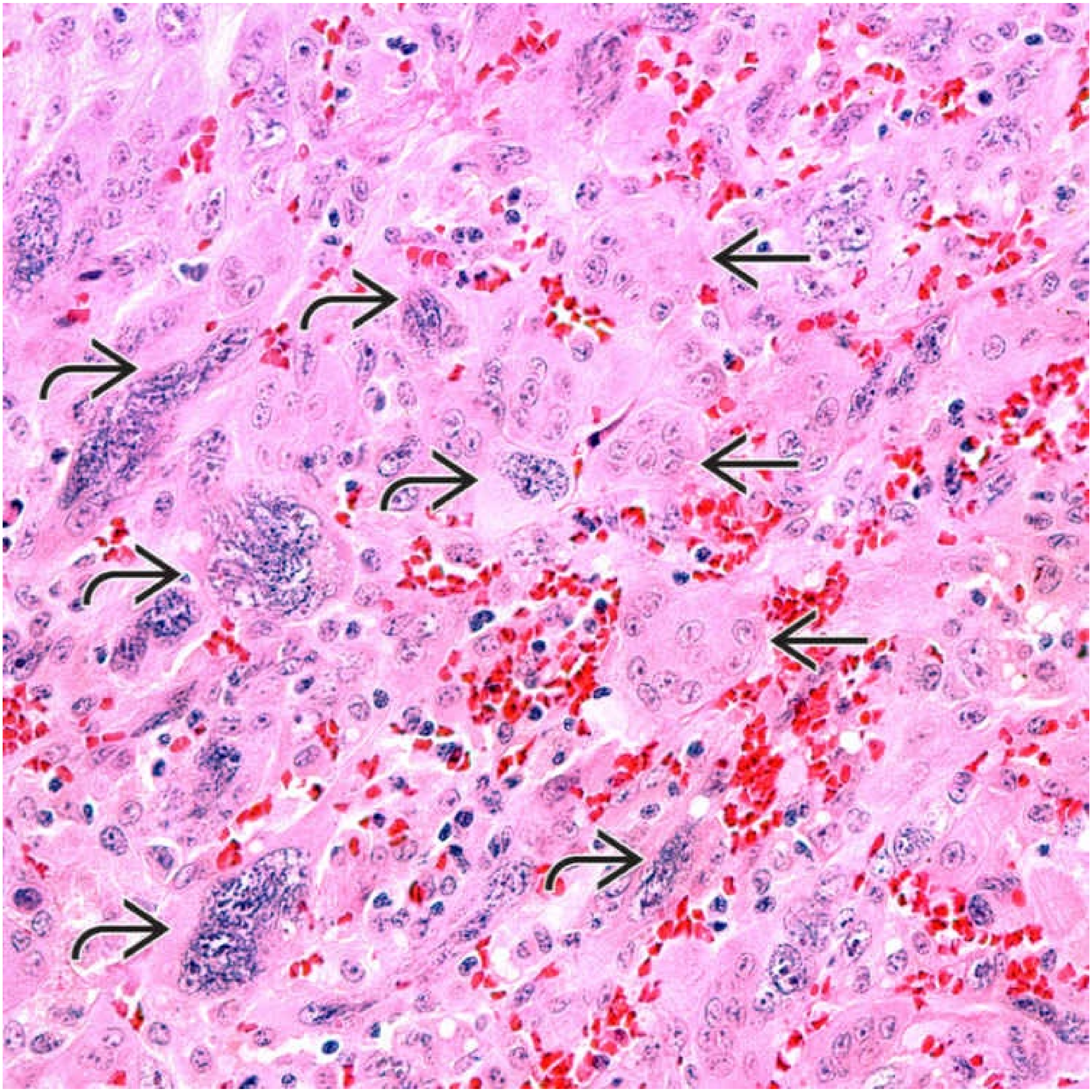
• Choriocarcinoma
• Metastatic undifferentiated carcinoma
• Other causes of multinucleated giant cells



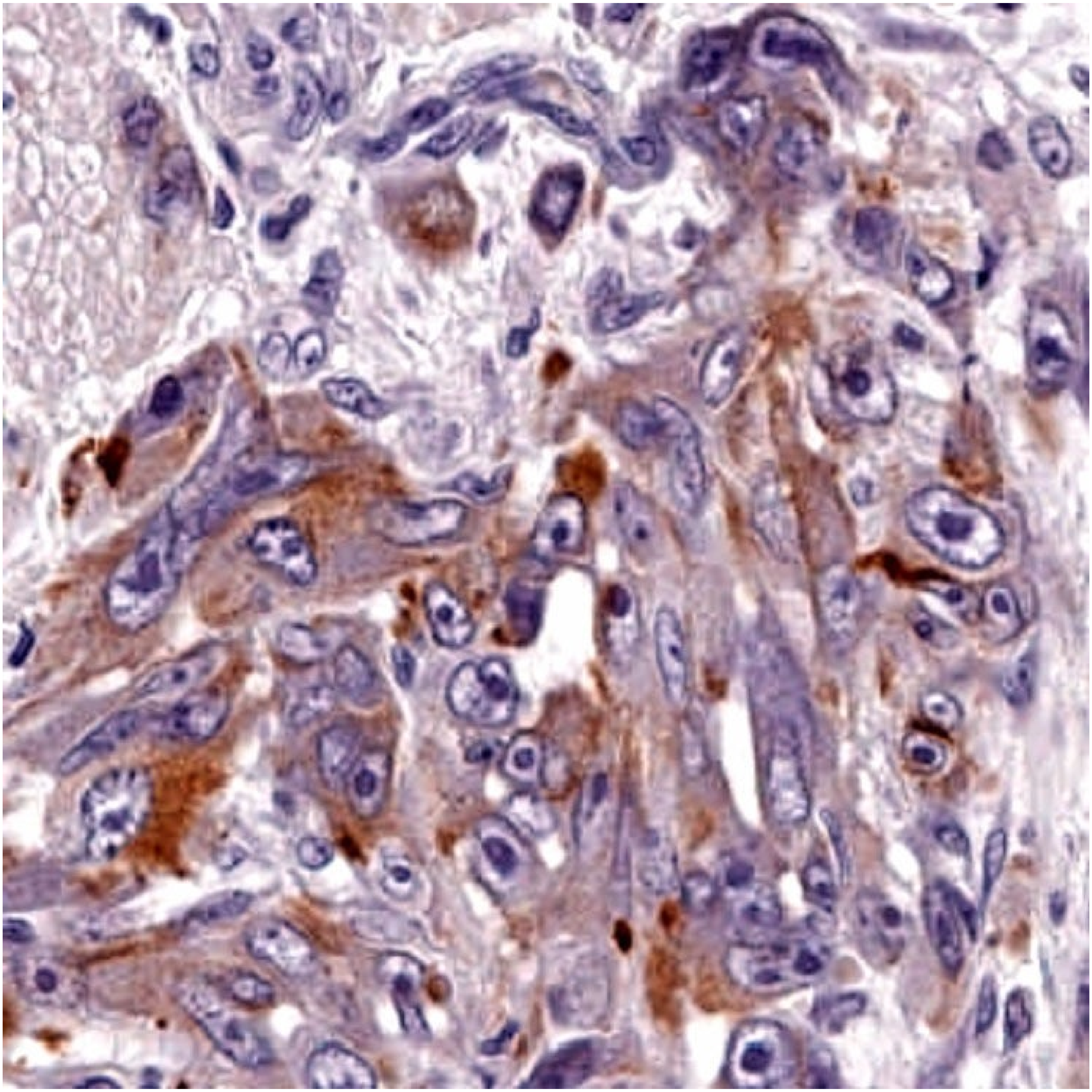
Soft Fleshy Mass
Gross photograph of an undifferentiated carcinoma with osteoclast-like giant cells shows a soft, fleshy cut surface with prominent hemorrhage and necrosis. Some cases can have a cystic appearance.



Spindle Cell Area
This undifferentiated carcinoma has a prominent sarcomatoid component featuring plump spindle cells in a fascicular pattern. This tumor can have a variable mix of anaplastic, sarcomatoid, and giant cell components.



Giant Cells
Undifferentiated carcinoma with osteoclast-like giant cells contains 2 cell populations: Large atypical multinucleated or mononuclear malignant cells ↱ and benign osteoclast-like giant cells → .



Keratin Immunohistochemistry
Undifferentiated carcinoma frequently demonstrates pankeratin expression in the large, atypical mononuclear cells. The positivity may be focal in some cases.

TERMINOLOGY

Synonyms

- Pleomorphic carcinoma, pleomorphic large cell carcinoma, pleomorphic giant cell carcinoma
  - Undifferentiated carcinoma with osteoclast-like giant cells
    - Giant cell tumor of pancreas
    - Osteoclast-like giant cell tumor of pancreas

Definitions

- Malignant epithelial neoplasm with significant component showing no definite differentiation
  - Wide range of morphologic findings ranging from pleomorphic epithelioid cells to multinucleated giant cells to spindle cells
  - Multiple patterns often present within same tumor

CLINICAL ISSUES

Epidemiology

- Incidence
  - Rare (< 1% of pancreatic neoplasms)
- Age
  - Range: 25-96 years; average: 60s
- Sex
  - Undifferentiated carcinoma: 3:1 male predominance
  - Undifferentiated carcinoma with osteoclast-like giant cells: Slight female predominance

Presentation

- Abdominal pain, palpable mass
- Weight loss, fatigue, nausea, vomiting

Treatment

- Surgical resection with curative intent
- Vast majority present with unresectable tumors

Prognosis

- Dismal, often < 1 year
- Longer survival has been observed in some cases

MACROSCOPIC

General Features

- Very large, fleshy mass with hemorrhage and necrosis
  - Average: 9-10 cm; anywhere in pancreas
- Often infiltrates adjacent organs

MICROSCOPIC

Histologic Features

- Heterogeneous features including anaplastic, giant cell, and spindle cell (sarcomatoid) components
  - Anaplastic component
    - Relatively monotonous, pleomorphic mononuclear cells and multinucleated giant cells with bizarre nuclei and abundant eosinophilic cytoplasm
    - Numerous mitoses
    - May be associated with dense neutrophilic infiltrate, cannibalism/emperipolesis of tumor cells
    - Scant desmoplasia, extensive necrosis and hemorrhage
  - Sarcomatoid component
    - Plump spindle cells in fascicular or herringbone pattern with relatively minimal stroma
    - Significant atypia, mitoses, and extensive necrosis
    - Heterologous elements such as bone, cartilage, and striated muscle may be seen in some cases
  - > 1/2 of undifferentiated carcinomas contain glandular component, and 1/4 to 1/3 have focal squamous differentiation
- Undifferentiated carcinoma with osteoclast-like giant cells
  - Mixture of osteoclast-like giant cells composed of benign-appearing multinucleated giant cells admixed with highly atypical neoplastic cells
    - Benign-appearing multinucleated osteoclast-like giant cells may have phagocytotic activity
    - Undifferentiated round to spindled atypical mononuclear cells have mitotic activity
  - May contain osteoid or focal chondroid differentiation
  - Often associated with mucinous cystic neoplasm or conventional adenocarcinoma

ANCILLARY TESTS

Immunohistochemistry

- CK7, CK8, CK18, and CK19 can be positive but usually focal
- Majority also express CEA, CA19-9, MUC1
- Neoplastic spindle cells may express smooth muscle actin but not desmin
- CD68, KP1, CD45, and α-1-antitrypsin can be positive in osteoclast-like giant cells

DIFFERENTIAL DIAGNOSIS

Melanoma

- Tumors with prominent anaplastic large cell component can mimic melanoma
- S100, HMB-45, Melan-A positive

Choriocarcinoma

- Tumors with prominent anaplastic large cell component can mimic choriocarcinoma

- β-HCG positive
- Affects younger patients

Metastatic Undifferentiated Carcinoma

- Less often associated with other pancreatic tumors, such as mucinous cystic neoplasm
- Imaging may be required to confirm primary site

Other Causes of Multinucleated Giant Cells

- Pseudocysts, infection, reaction to tumor, other malignant neoplasms (lymphoma, sarcoma)
- Giant cells in these conditions are either benign or malignant, but both populations are not present

SELECTED REFERENCES

1. Gulati, A, et al. Undifferentiated carcinoma of pancreas with osteoclast-like giant cells mimicking a pseudopancreatic cyst. *J Cancer Res Ther*. 2015; 11(4):1046.
2. Yonemasu, H, et al. Phenotypical characteristics of undifferentiated carcinoma of the pancreas: a comparison with pancreatic ductal adenocarcinoma and relevance of E-cadherin, alpha catenin and beta catenin expression. *Oncol Rep*. 2001; 8(4):745–752.
3. Hoorens, A, et al. Undifferentiated carcinoma of the pancreas: analysis of intermediate filament profile and Ki-ras mutations provides evidence of a ductal origin. *J Pathol*. 1998; 185(1):53–60.

Squamous/Adenosquamous Carcinoma, Pancreas

KEY FACTS

Terminology

- Pure squamous or mixed glandular and squamous carcinoma of pancreas
- Uncommon variant of pancreatic cancer with both glandular and squamous differentiation

Clinical Issues

- Adenosquamous carcinoma accounts for 3-4% of exocrine pancreas malignancies
- Pure squamous cell carcinoma is vanishingly rare
- Extremely poor survival
- Extremely poor with median survival period of 6 months
- Surgical resection

Microscopic

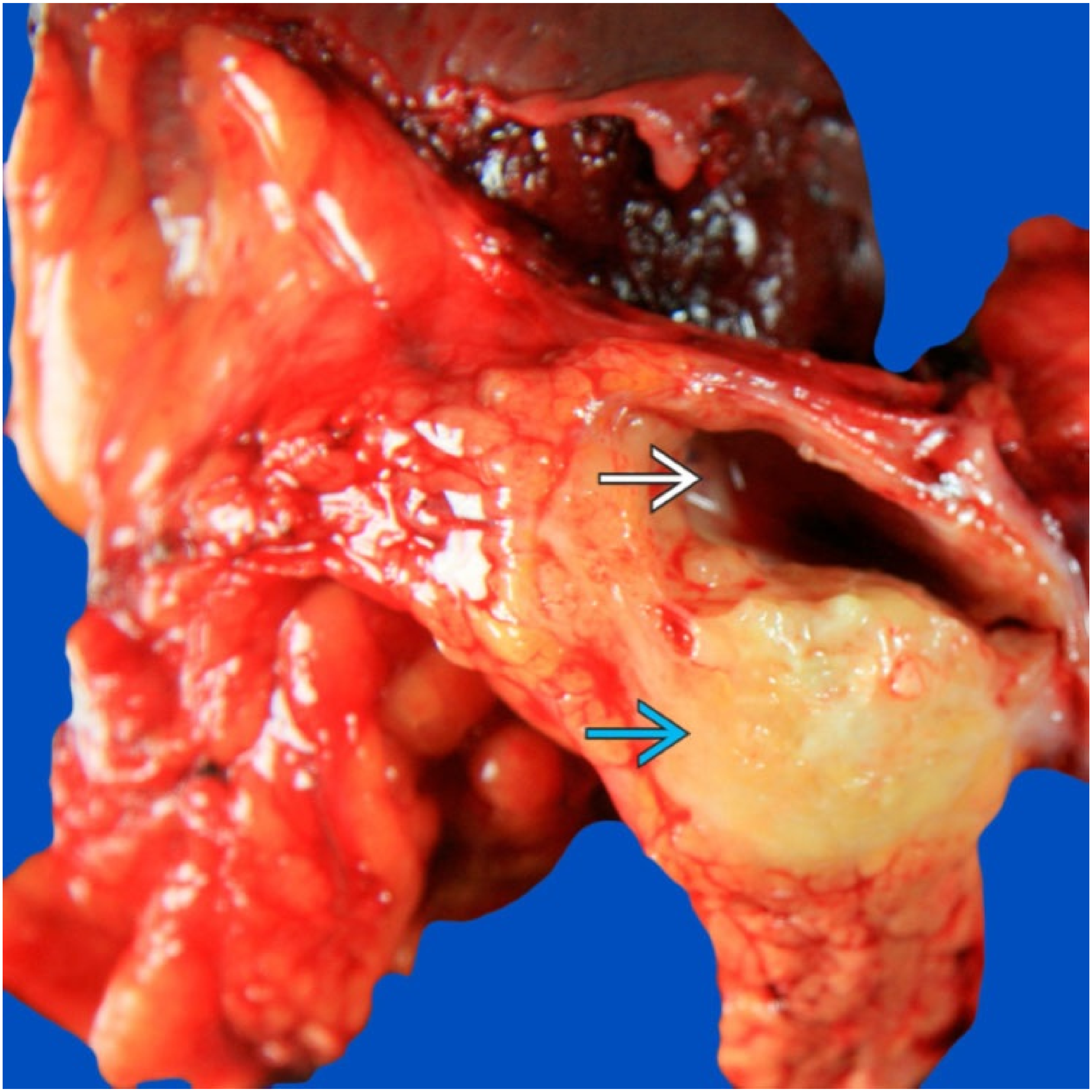
- Squamous cell carcinoma exhibits only squamous component
  - Adenosquamous carcinoma has malignant glandular and squamous components
    - Glandular component may contain conventional ductal-type, clear cell, or signet ring cell components

Ancillary Tests

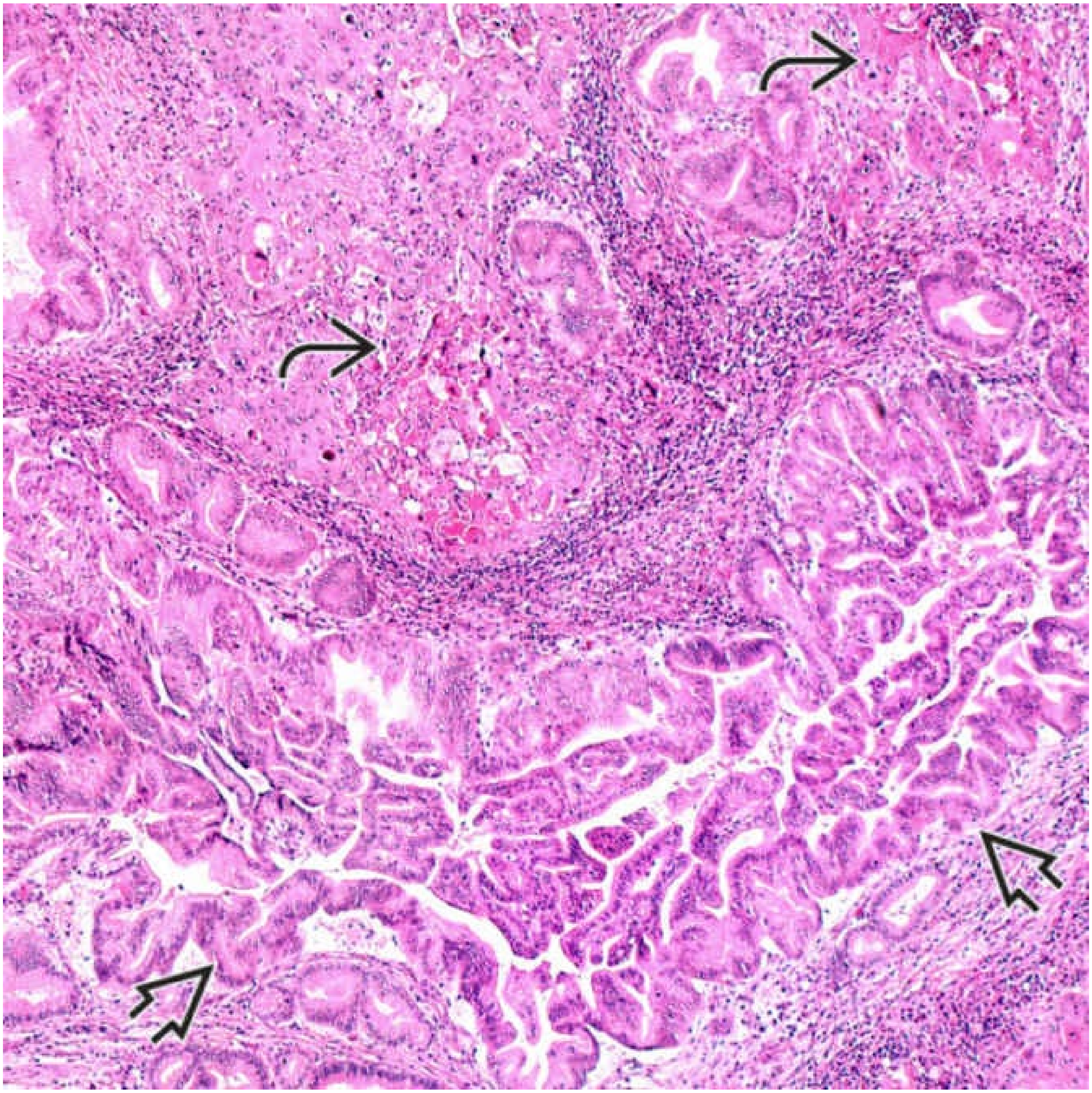
- p63 is positive in squamous component
- Mucin stain, CK7, CK20, CEA, and CA19-9 highlight adenocarcinoma component

Top Differential Diagnoses

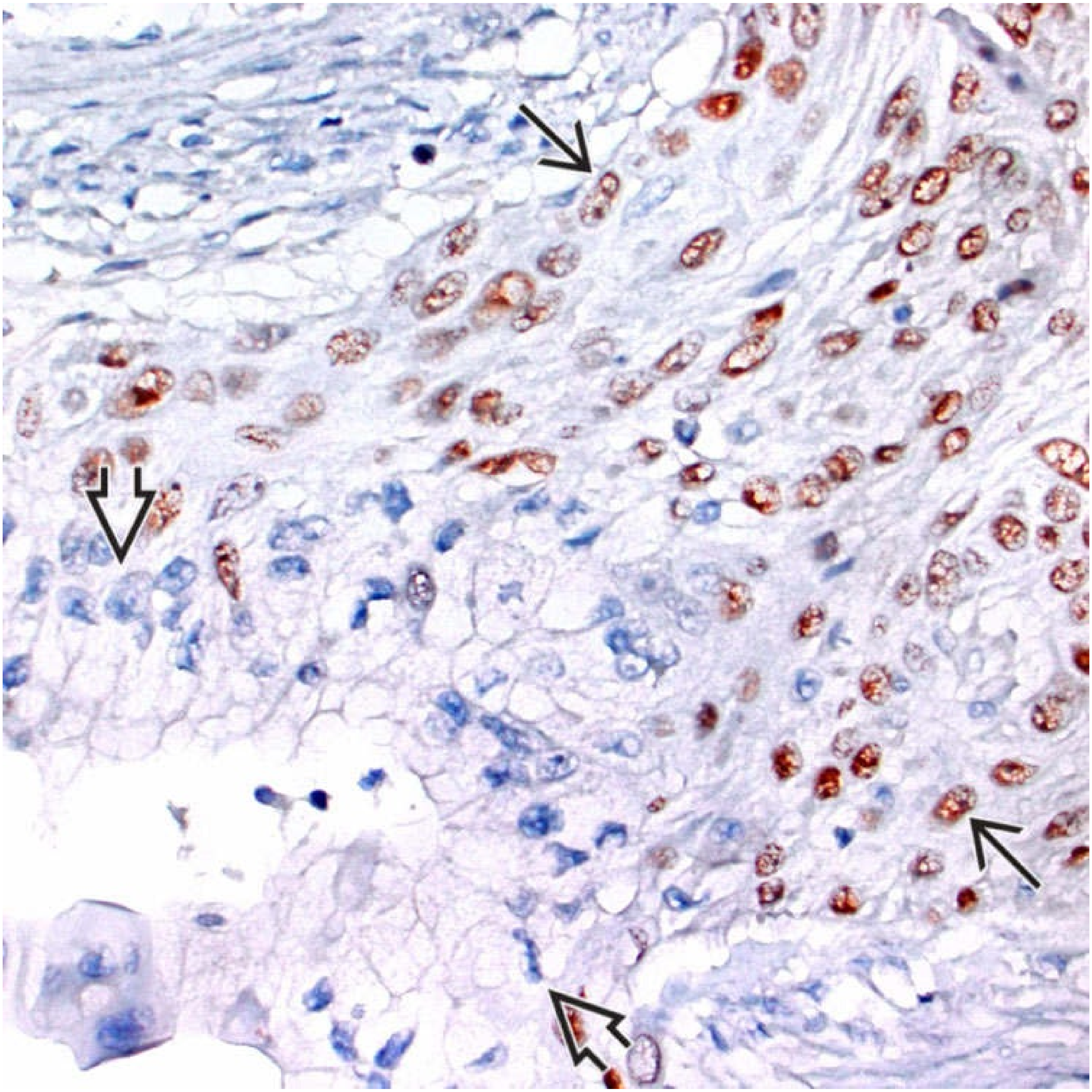
- Metastatic squamous cell carcinoma
- Pancreatoblastoma



Solid-Cystic Mass
Primary adenosquamous cell carcinoma in the tail of the pancreas shows a relatively well-demarcated, tan-white to yellow solid mass → with a cystic component ⇒ .

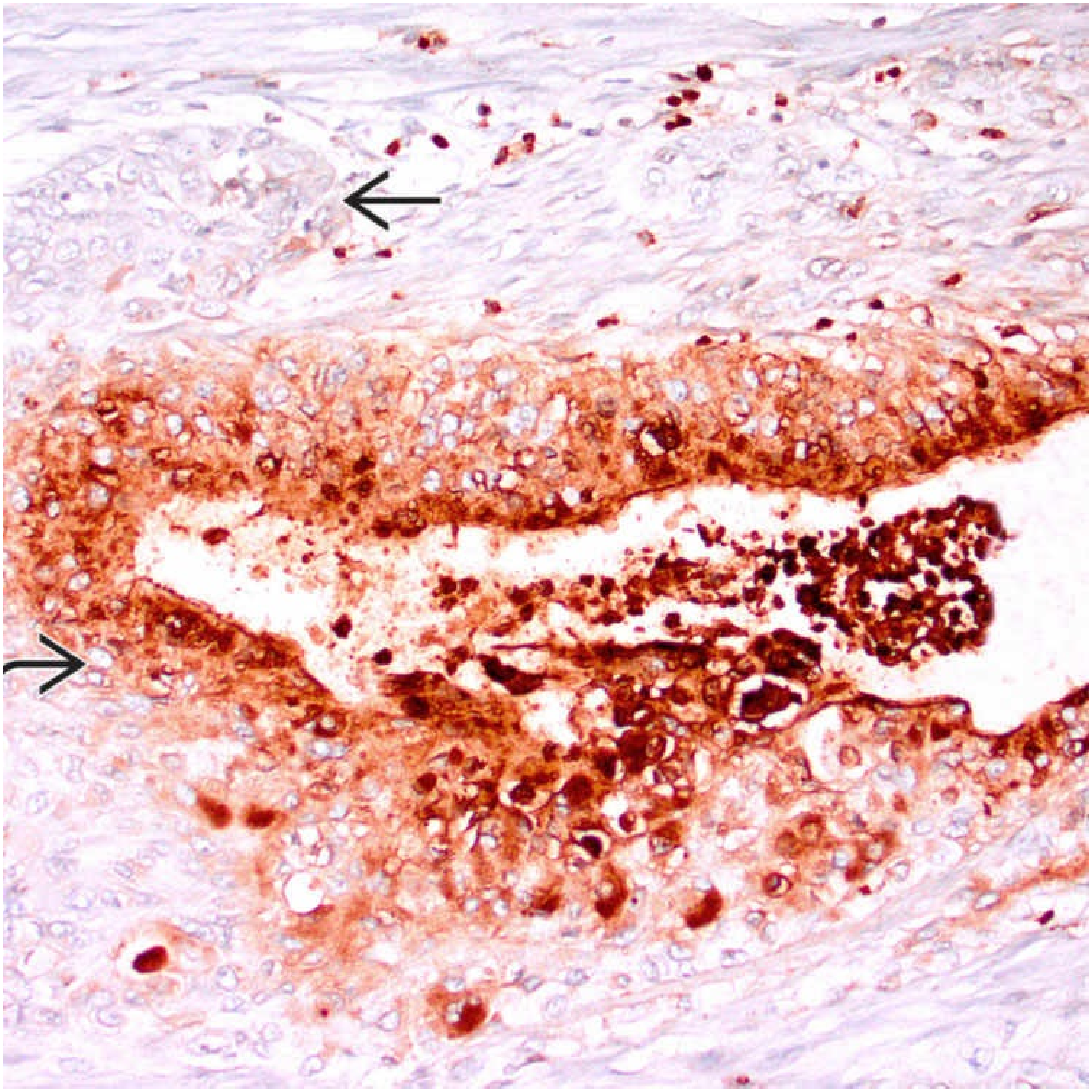


Squamous and Glandular Areas
Adenosquamous cell carcinoma of the pancreas demonstrates islands of malignant squamous cells with keratinization adjacent to high-grade pancreatic intraepithelial neoplasia involving an interlobular duct .



p63 Stain

Immunohistochemical stain for p63 shows nuclear staining in the squamous component → of adenosquamous cell carcinoma, while the glandular component is negative ⇨ .



CEA Stain
Immunohistochemical stain for carcinoembryonic antigen highlights the glandular component, while the squamous component is negative.

TERMINOLOGY

Synonyms

- Adenoacanthoma
- Mixed squamous/adenocarcinoma
- Mucoepidermoid carcinoma

Definitions

- Uncommon variant of pancreatic cancer with both glandular and squamous differentiation
  - Pure squamous cell carcinoma of pancreas is vanishingly rare

ETIOLOGY/PATHOGENESIS

Neoplastic

- A few hypotheses attempt to explain origin of squamous component
  - Squamous metaplasia of pancreatic duct epithelium
  - Both components derive from common progenitor

CLINICAL ISSUES

Epidemiology

- Incidence
  - Adenosquamous carcinoma accounts for 3-4% of malignancies of exocrine pancreas
  - Pure squamous cell carcinoma reportedly accounts for up to 0.7% of pancreatic carcinoma
- Age
  - Mean: 63 years
  - Range: 28-86 years
- Sex
  - M:F = 1.5:1.0

Presentation

- Similar to conventional ductal adenocarcinoma of pancreas
  - Weight loss
  - Painless jaundice
  - Other abdominal symptoms

Treatment

- Surgical resection

Prognosis

- Extremely poor with median survival period of 6 months
- Mean survival of 11 months even in patients with surgically resectable tumors

IMAGING

General Features

- Similar to conventional pancreatic ductal adenocarcinoma

MACROSCOPIC

General Features

- Firm, ill-defined, tan to white mass ± cystic component
- Most arise in head of pancreas but can also arise in body or tail or even diffusely involve entire gland

Size

- Large (mean: ~ 6 cm)

MICROSCOPIC

Histologic Features

- Squamous cell carcinoma exhibits only squamous component
  - Adenosquamous carcinoma has malignant glandular and squamous components
  - Glandular component usually consists of conventional adenocarcinoma
  - May have clear cell or signet ring cell components
- Squamous cell carcinoma shows nests or sheets of neoplastic cells with whorls, keratin pearls, individual cell keratinization, &/or intercellular bridges
- 2 components can be intimately admixed or topographically separate

Cytologic Features

- Various proportions of cells with glandular or squamous features on smear
- Pure squamous cell carcinoma may be undersampling of adenosquamous cell carcinoma or metastatic squamous cell carcinoma from another organ

ANCILLARY TESTS

Histochemistry

- Mucicarmine
  - Reactivity: Positive in glandular component
  - Staining pattern: Intracytoplasmic mucin

Immunohistochemistry

- p63
  - Positive in squamous component

- CK7, CK20, CEA, and CA19-9
    - Usually restricted to glandular component

DIFFERENTIAL DIAGNOSIS

Metastatic Squamous Cell Carcinoma

- Clinical history of extrapancreatic squamous cell carcinoma
- Absence of glandular differentiation

Pancreatoblastoma

- Predominant acinar component in addition to squamoid nests ± glandular elements

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Pure squamous cell carcinomas of pancreas are extremely rare
- Adequate sectioning may reveal glandular component in tumors with dominant squamous morphology

SELECTED REFERENCES

1. Voong, KR, et al. Resected pancreatic adenosquamous carcinoma: clinicopathologic review and evaluation of adjuvant chemotherapy and radiation in 38 patients. *Hum Pathol*. 2010; 41(1):113–122.
2. Brody, JR, et al. Adenosquamous carcinoma of the pancreas harbors KRAS2, DPC4 and TP53 molecular alterations similar to pancreatic ductal adenocarcinoma. *Mod Pathol*. 2009; 22(5):651–659.

Serous Cystadenoma

KEY FACTS

Terminology

- Benign, cystic epithelial neoplasm

Clinical Issues

- Discovered because of abdominal mass &/or pain or incidentally
- Most likely in female patient in 6th decade of life

Macroscopic

- Discrete, well-demarcated lesion composed of numerous thin-walled cysts filled with serous fluid (microcystic)
- Less common variants: Solid, oligocystic (macrocystic)

Microscopic

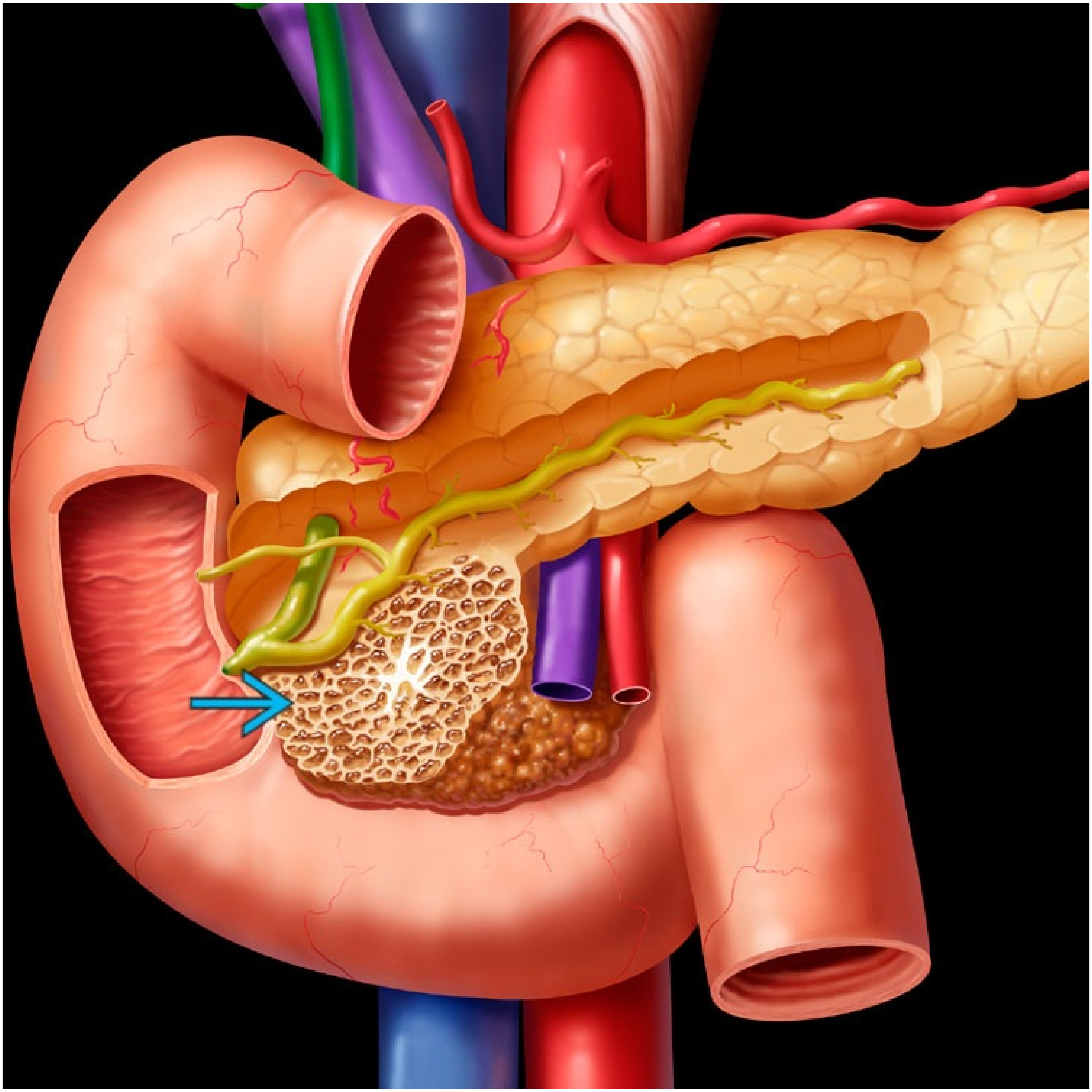
- Cysts typically lined by single layer of cuboidal to flat epithelial cells
  - Clear to pale cytoplasm with sharp cell border
  - Small, round to oval, uniform nuclei
  - Periodic acid-Schiff without diastase has granular cytoplasmic staining
- Exuberant rich capillary network immediately adjacent to epithelium
- May have stellate scar that can be calcified

Ancillary Tests

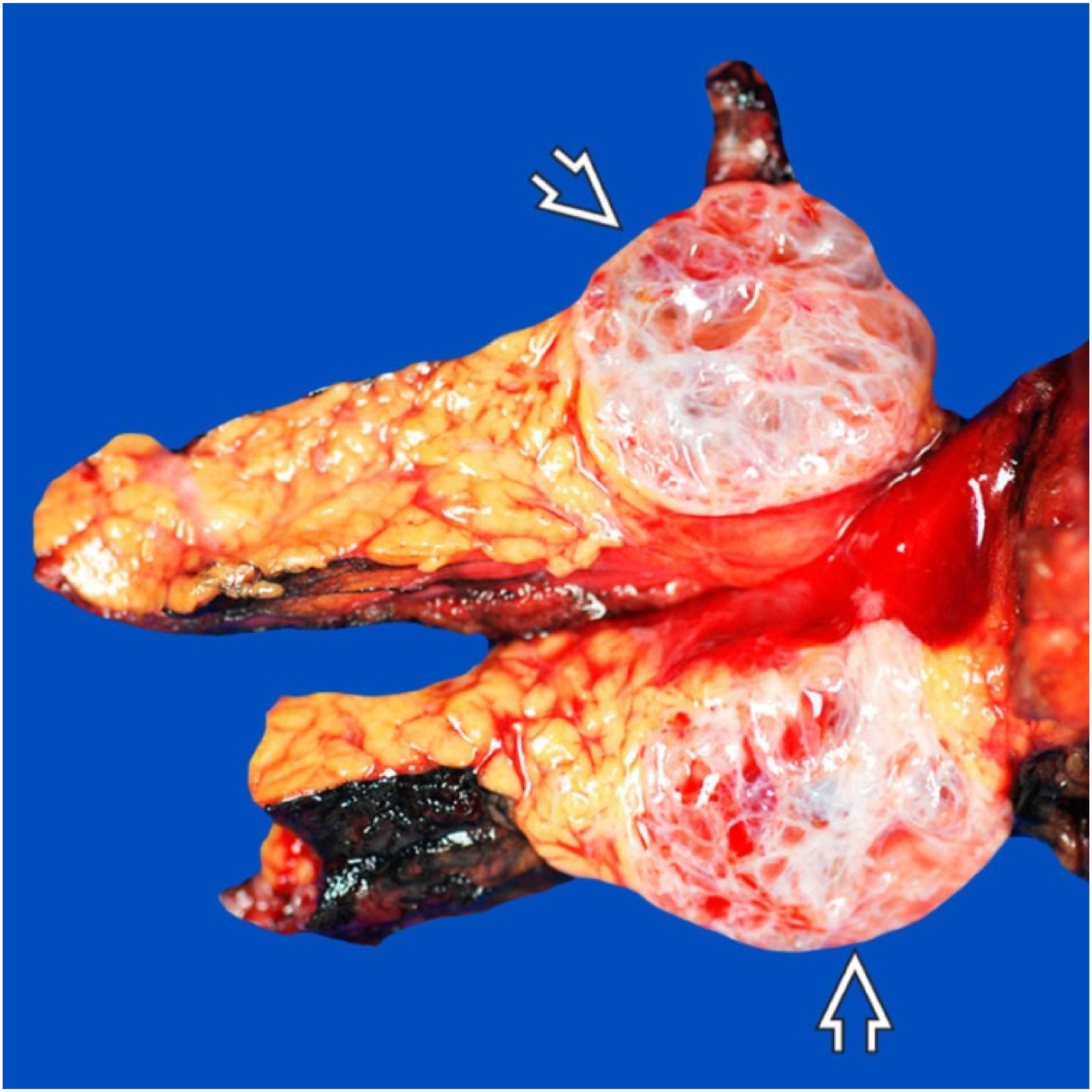
- Immunohistochemical reactivity
  - Cytokeratin, α-inhibin, calponin, GLUT1, MUC6 (+)
- von Hippel-Lindau (*VHL*) gene alteration detected even in sporadic cases

Top Differential Diagnoses

- von Hippel-Lindau-associated pancreatic cysts
- Serous cystadenocarcinoma
- Pseudocyst
- Mucinous cystic neoplasm
- Metastatic clear cell renal cell carcinoma

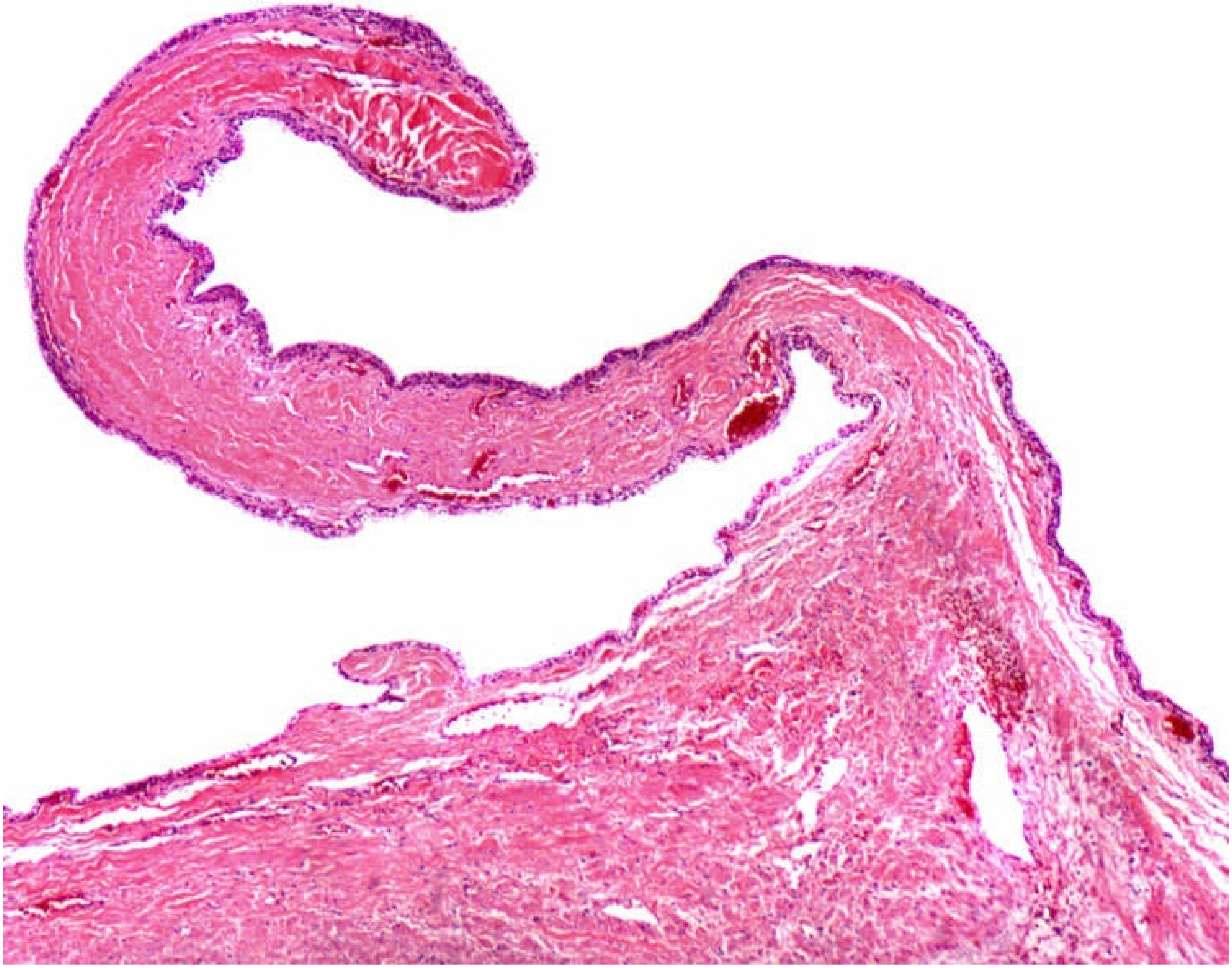


Graphic Representation
Sponge-like or “honeycomb” mass in the pancreatic head → is shown. Note the presence of innumerable small cysts and central scar. The pancreatic duct is not obstructed.

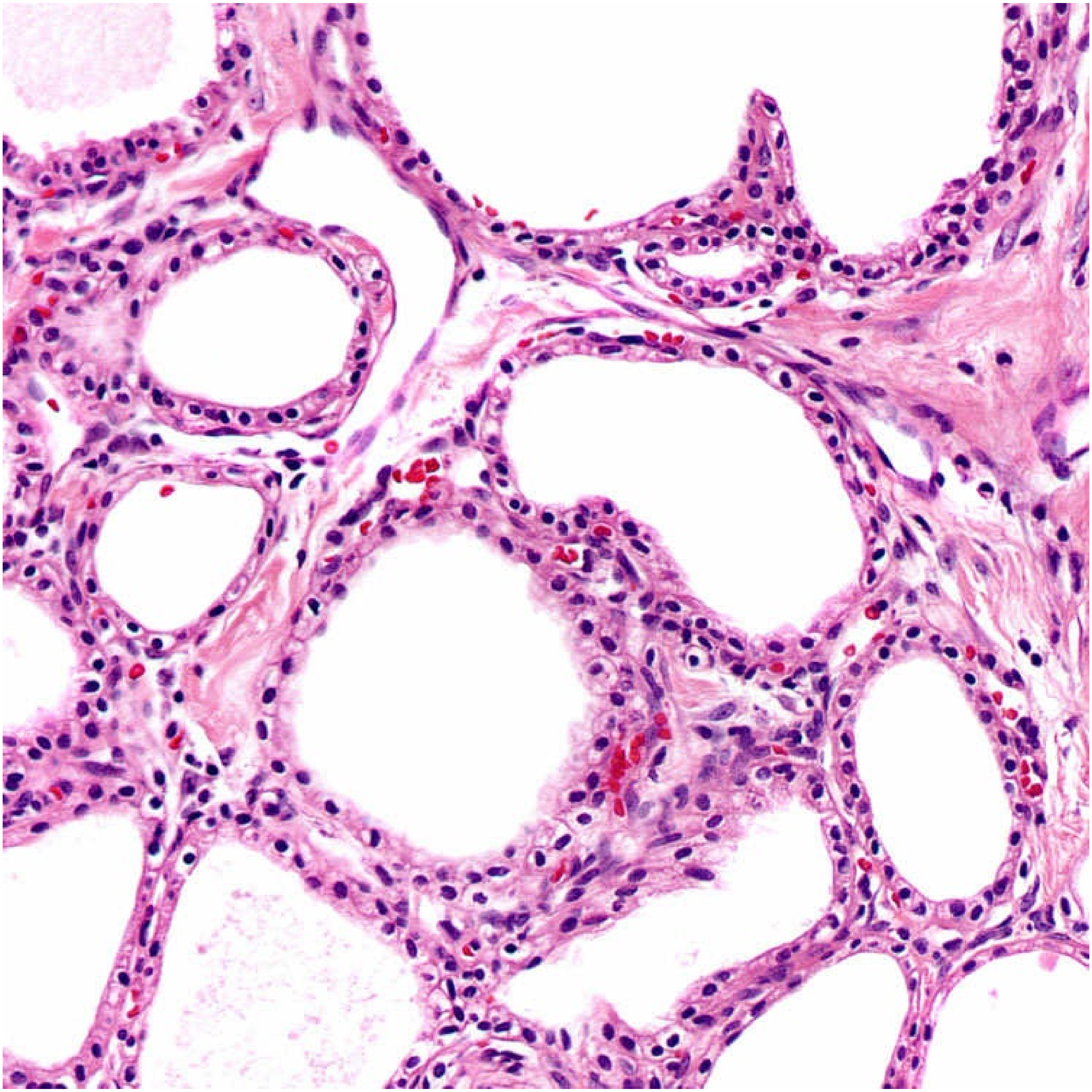


Honeycomb Appearance

Round, well-circumscribed mass ⇨ is shown in the tail of the pancreas with compact, small, thin, smooth-walled cysts containing clear serous fluid. The cysts did not communicate with the pancreatic duct.



Flat Lining Epithelium
The lining epithelium of the cyst is comprised of a single layer of epithelial cells that rests on a fibrous cyst wall.



Multiloculated Appearance
In its most typical presentation, serous cystadenoma is composed of multiple microcysts lined by bland cuboidal epithelium. The lining cells usually have pale cytoplasm. The presence of congested capillaries adjacent to the epithelial cells is a characteristic feature.

TERMINOLOGY

Abbreviations

- Serous cystadenoma (SCA)

Synonyms

- Serous microcystic adenoma

- Clear cell or glycogen-rich adenoma

Definitions

- Benign, cystic epithelial neoplasm
  - Presumably originates from centroacinar cell/intercalated duct system

ETIOLOGY/PATHOGENESIS

No Uniform Consensus on Cellular Origin

- Acinar, centroacinar, and ductal origins have all been considered
  - Some immunohistochemical and ultrastructural features suggest centroacinar cell origin

CLINICAL ISSUES

Epidemiology

- Incidence
  - 10% of surgically resected cystic pancreatic lesions
- Age
  - Mean: 66 years; range: 18-91 years
  - Rarely reported in infants (oligocystic variant)
- Sex
  - F:M ratio ranges from 3:1 to 7:3

Site

- Anywhere in pancreas

Presentation

- 2/3 of patients: Abdominal mass &/or pain
  - Larger SCA (> 4 cm) more likely to give rise to symptoms
- 1/3 of patients: Asymptomatic, incidentally discovered

Treatment

- Surgical resection if symptomatic

Prognosis

- Excellent, recurs in < 2% of cases

IMAGING

Radiographic Findings

- Grayscale ultrasound and contrast-enhanced computed tomography are best imaging modalities
  - Well-defined mass
  - Microlacunae separated by delicate septa
  - – Enhancement of septa on computed tomography

- Central stellate scar

– Echogenic area that may be calcified resulting in sunburst appearance on ultrasound

MACROSCOPIC

General Features

- Discrete, well-demarcated, slightly bosselated tumor
  - Variably sized, thin-walled cysts filled with clear, watery, or straw-colored fluid
  - No communication of cyst to pancreatic ductal system
- Microcystic (most common growth pattern)
  - Sponge-like or honeycomb appearance
  - Numerous tightly packed cysts, 0.1 to < 1 cm
  - Central stellate fibrous scar, which may be calcified

Size

- Usually < 5 cm but can be up to 25 cm

Variants

- Solid variant
  - Well-demarcated, solid mass with thick fibrous bands
- Oligocystic (macrocystic, megacystic) variant (20% of cases)
  - Larger (peripheral) admixed with smaller cysts (central)
  - No central scar
  - Often in pancreatic head

MICROSCOPIC

Histologic Features

- Variably sized cysts lined by single-layered cuboidal/flat epithelium
  - Rarely, microscopic papillary tufts without fibrovascular cores or true papillae with fibrovascular cores
  - Solid variant can have solid nests of cells and small acini
- Cells are uniform and lack atypia and mitotic activity

- Clear to pale cytoplasm, abundant cytoplasmic glycogen
  - Rarely have eosinophilic (oncocyte-like) cytoplasm
  - Well-defined cytoplasmic borders
  - Small, round to oval, uniform nuclei
    - Dense homogeneous chromatin
    - Can have nuclear enlargement
    - Inconspicuous nucleoli
- Rich capillary network intimately admixed with epithelium
  - Red blood cells appear interspersed with epithelium
- Can have stellate scar, which may become calcified

Cytologic Features

- All variants are cytologically similar
  - No atypia, necrosis, or mitotic activity

Predominant Pattern/Injury Type

- Cystic

Predominant Cell/Compartment Type

- Epithelial: Serous cells

ANCILLARY TESTS

Cytology

- Clear, thin fluid; may be bloody
- Generally paucicellular or acellular
- Epithelial cells form small groups and flat sheets, should be distinguished from gastrointestinal epithelium

Histochemistry

- Granular cytoplasmic positivity with periodic acid-Schiff stain
- Negative with periodic acid-Schiff with diastase stain

Antibody	Reactivity	Staining Pattern	Comment
AE1/AE3	Positive	Cytoplasmic	
CK7	Positive	Cytoplasmic	
CK8/18/CAM5.2	Positive	Cytoplasmic	
CK19	Positive	Cytoplasmic	
Inhibin-α	Positive	Cytoplasmic	76-92%
Calponin	Positive	Cytoplasmic	85%
MUC6	Positive	Cytoplasmic	60-85%
GLUT1	Positive	Cell membrane	94%; may not have diffuse staining
EMA	Positive	Cytoplasmic	33%
MUC1	Positive	Cytoplasmic	24-38%
VEGF	Positive	Cell membrane and cytoplasm	50% of cases; may be responsible for rich vascularity in this lesion
CA9	Positive	Cell membrane	

Immunohistochemistry

- Cytokeratin and GLUT-1 (+)
- Vimentin, CEA, HMB-45, melan-A, MUC5, chromogranin, trypsin (-)
- Usually MUC2, synaptophysin (-) (positive in < 5% of SCA)

Genetic Testing

- von Hippel-Lindau (*VHL*) gene alteration detected in 40-70% of sporadic cases
  - Loss of heterozygosity at chromosome 3p25
  - *VHL* gene germline mutation

DIFFERENTIAL DIAGNOSIS

von Hippel-Lindau-Associated Pancreatic Cysts

- Autosomal dominant disorder characterized by clear cell neoplasms
  - Histologically identical to SCA, but distribution differs
  - Does not form distinct lesion
  - Irregularly scattered cysts in pancreas, multifocal or diffuse
- Some classify these together with nonsyndromic SCA; others designate them separately

Serous Cystadenocarcinoma

- Extremely rare, morphologically indistinguishable from SCA
- Shows extrapancreatic involvement: Spleen, stomach, duodenum, liver, lymph node, peritoneum

Pseudocyst

- Unilocular cyst with thick fibrous wall
- Sample entire cyst before rendering this diagnosis
- Oligocystic SCA with epithelial denudation following biopsy can mimic pseudocyst

Mucinous Cystic Neoplasm

- Often in female patients in pancreatic tail
- Multilocular, thick-walled cyst with mucoid material
- Ovarian-type stroma and overlying mucinous epithelium with variable degree of cytologic atypia
- Serous macrocystic adenoma can radiographically resemble mucinous cystic neoplasm

Lymphangioma

- Multilocular cyst lined by endothelial cells and lymphoid aggregates
- Immunoreactive for CD34, CD31, and D2-40
- SCA with attenuated epithelial lining can mimic this entity

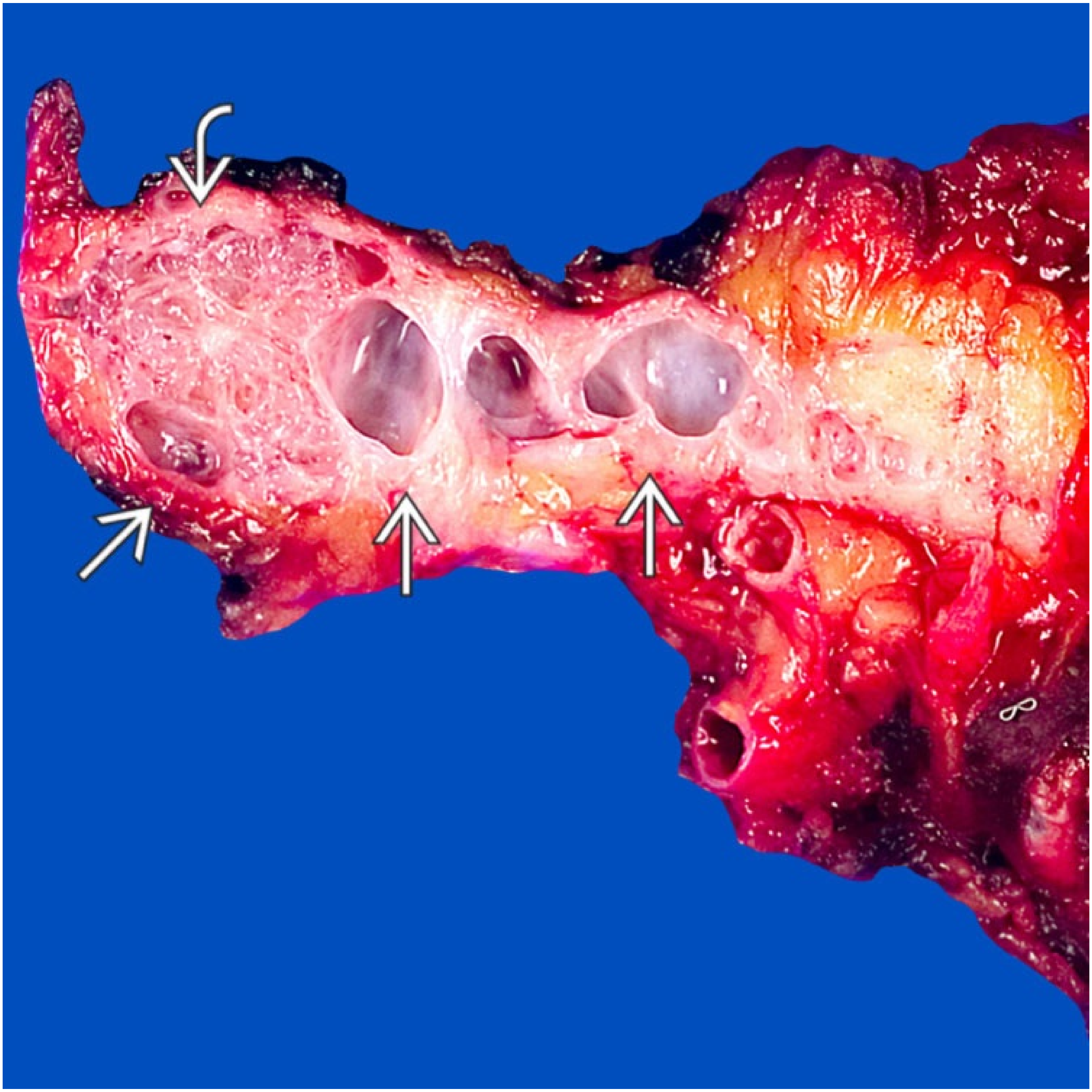
Metastatic Clear Cell Renal Cell Carcinoma

- Has glycogen-rich clear cells but is cytologically atypical
- Positive immunohistochemical staining for pax-2, pax-8, RCC

Combined Well-Differentiated Endocrine Neoplasm/Serous Cystadenoma

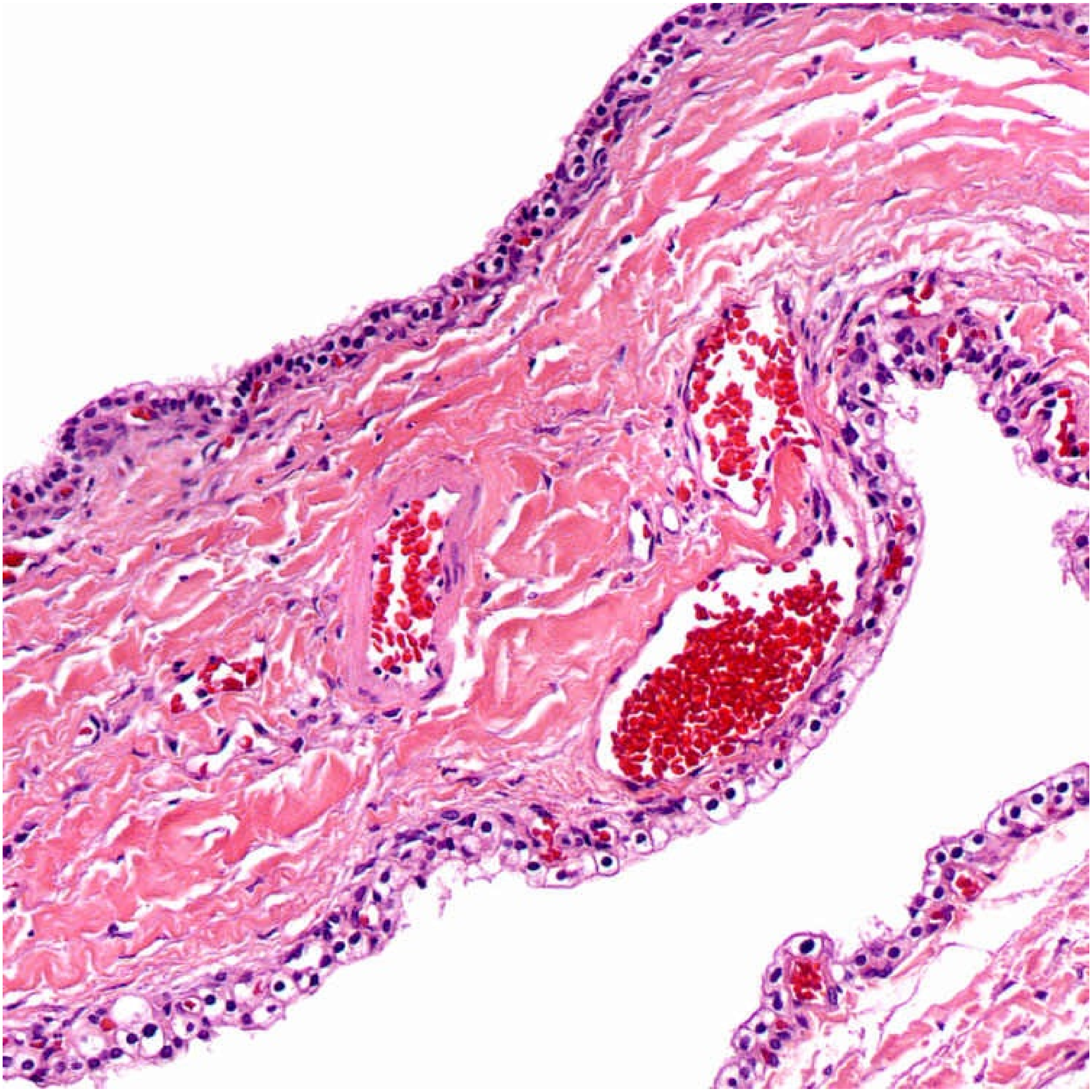
- Occurs in patients with von Hippel-Lindau syndrome
- Combination of adjacent or admixed, low-grade pancreatic neuroendocrine tumor and SCA

CT Findings
Transverse contrast-enhanced CT scan shows a well-defined enhancing mass in the pancreatic head. Foci of calcification and a hypodense center (scar/cystic component) are noted in the lesion.

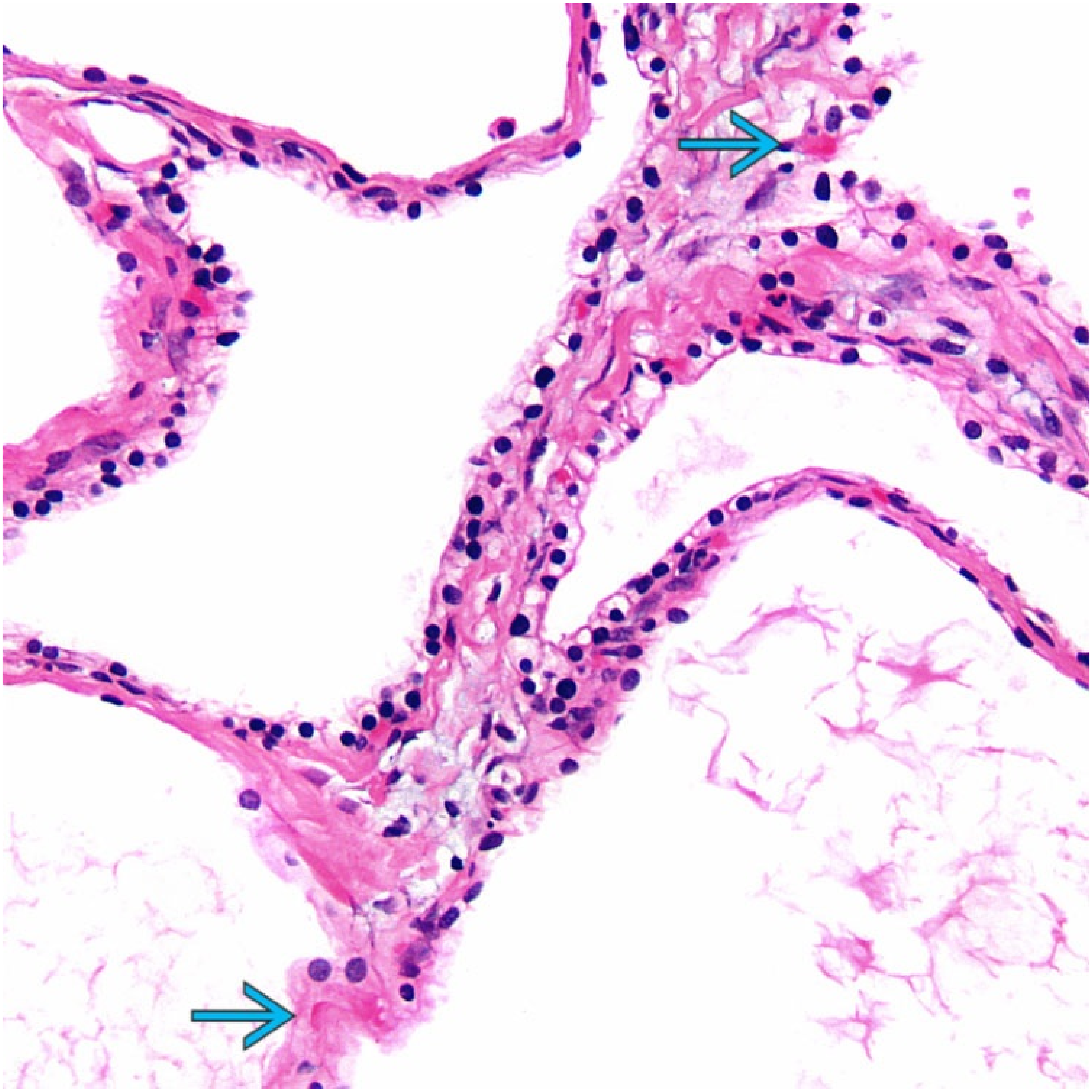


Oligocystic Variant

Oligocystic variant is shown in the distal pancreas (body and tail). The cysts are smaller in size in association with a scar, while larger cysts are present toward the periphery of the specimen .

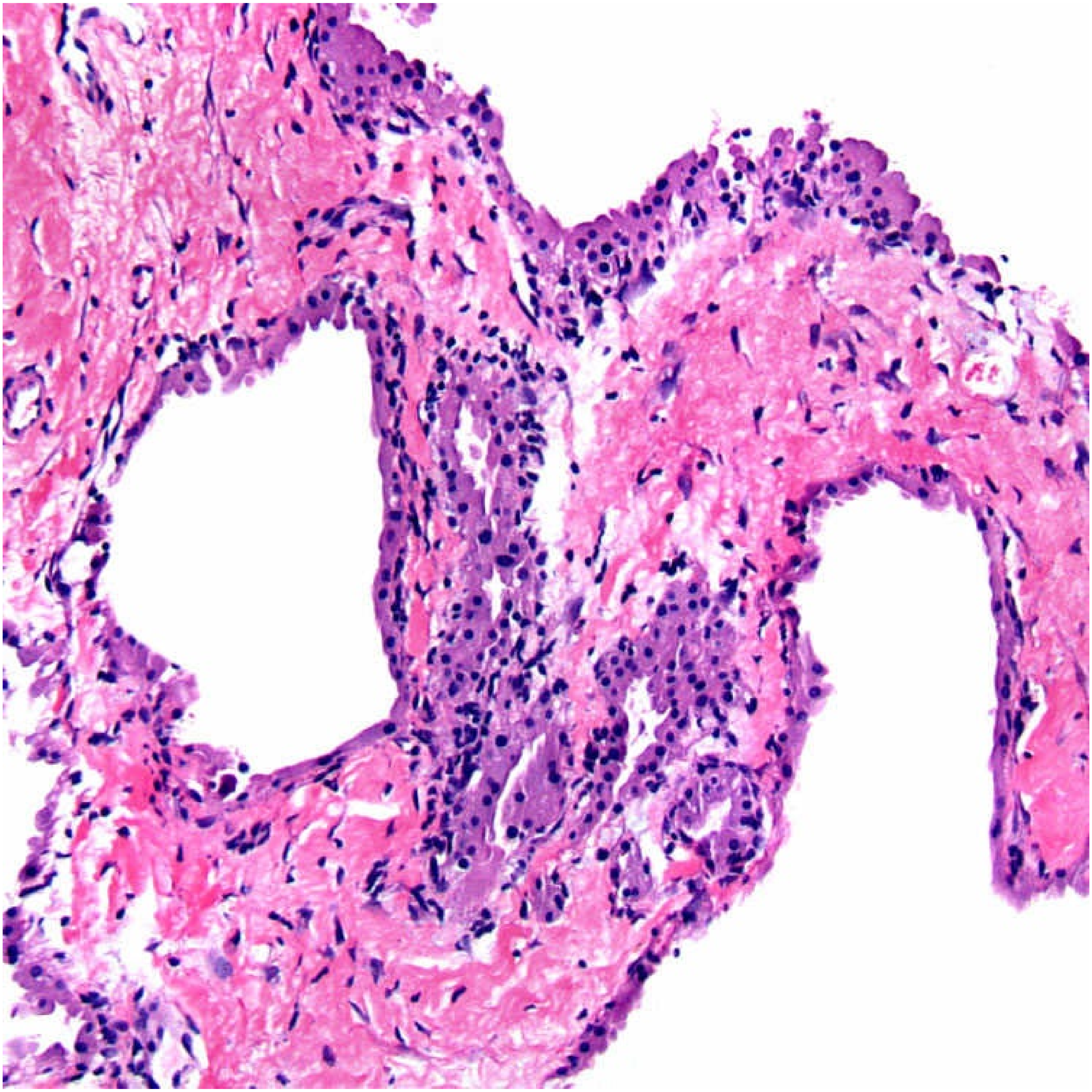


Serous Cystadenoma
The typical microscopic finding is that the lining epithelial cells of the cyst have clear glycogen-rich cytoplasm and lack cytologic or architectural atypia.



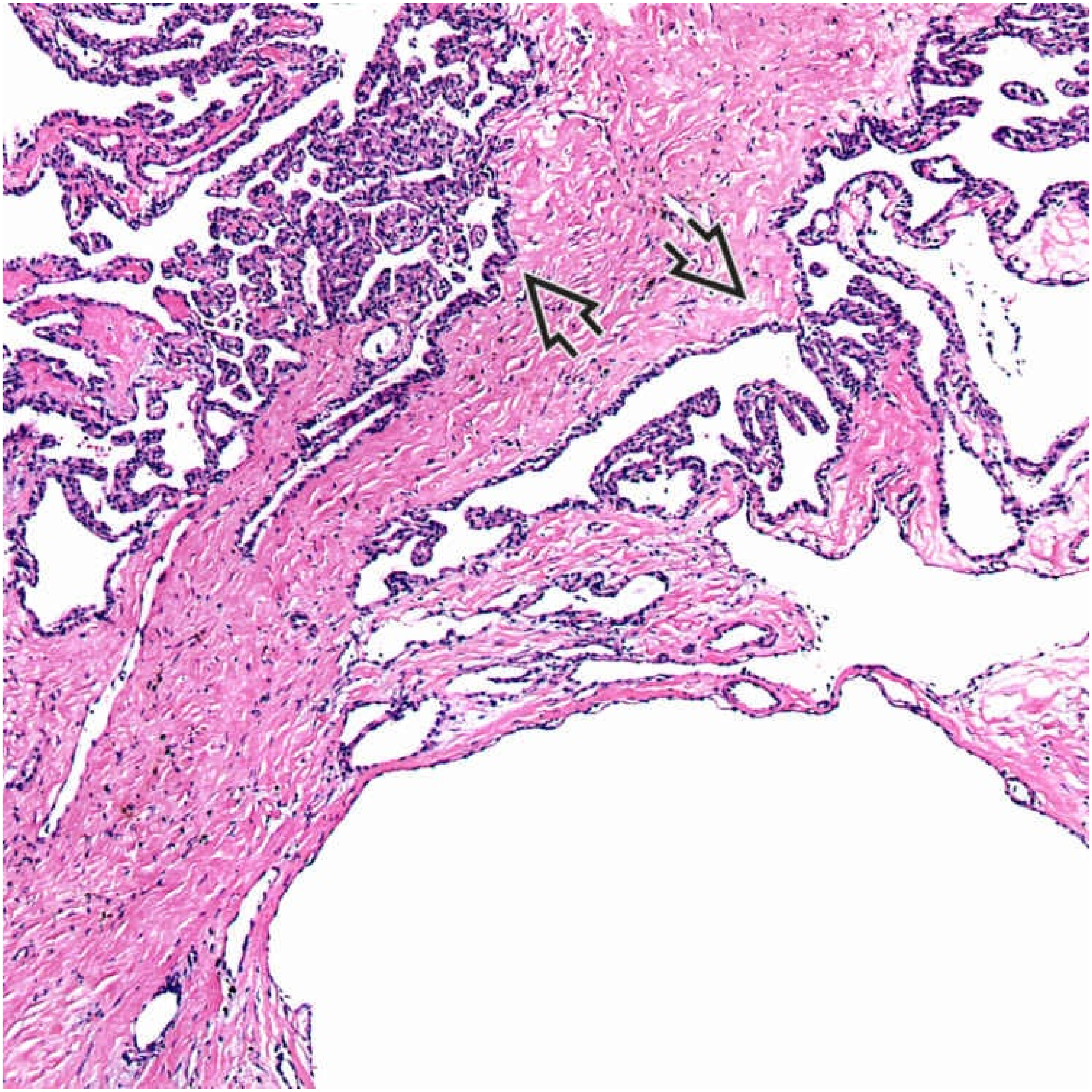
Rich Capillary Network

The small cysts can show proteinaceous fluid in the lumen. The subjacent rich capillary network → is better appreciated at higher magnification and is a highly characteristic feature of serous cystadenoma.



Oncocytic Cytoplasm

In some cases, the cysts of serous cystadenoma may be lined by epithelial cells with abundant granular eosinophilic (oncocyte-like) cytoplasm in contrast to the clear cytoplasm seen in the majority of cases.



Papillary Tufts
While the lining epithelium is flat in most cases, microscopic papillary tufts without fibrovascular cores project into the cyst lumen in rare cases.

SELECTED REFERENCES

1. Reid, MD, et al. Serous cystic neoplasms of the pancreas: clinicopathologic and molecular characteristics. *Semin Diagn Pathol*. 2014; 31(6):475–483.
2. Marsh, WL, et al. Calponin is expressed in serous cystadenomas of the pancreas but not in adenocarcinomas or endocrine tumors. *Appl Immunohistochem Mol Morphol*. 2009; 17(3):216–219.
3. Thirabanjasak, D, et al. Is serous cystadenoma of the pancreas a model of clear-cell-associated angiogenesis and tumorigenesis? *Pancreatology*. 2009; 9(1-2):182–188.

4. Wargo, JA, et al. Management of pancreatic serous cystadenomas. *Adv Surg*. 2009; 43:23–34.
5. Reese, SA, et al. Solid serous adenoma of the pancreas: a rare variant within the family of pancreatic serous cystic neoplasms. *Pancreas*. 2006; 33(1):96–99.
6. Matsumoto, T, et al. Malignant serous cystic neoplasm of the pancreas: report of a case and review of the literature. *J Clin Gastroenterol*. 2005; 39(3):253–256.
7. Kosmahl, M, et al. Serous cystic neoplasms of the pancreas: an immunohistochemical analysis revealing alpha-inhibin, neuron-specific enolase, and MUC6 as new markers. *Am J Surg Pathol*. 2004; 28(3):339–346.
8. Perez-Ordonez, B, et al. Solid serous adenoma of the pancreas. The solid variant of serous cystadenoma? *Am J Surg Pathol*. 1996; 20(11):1401–1405.
9. George, DH, et al. Serous cystadenocarcinoma of the pancreas: a new entity? *Am J Surg Pathol*. 1989; 13(1):61–66.
10. Alpert, LC, et al. Microcystic adenoma (serous cystadenoma) of the pancreas. A study of 14 cases with immunohistochemical and electron-microscopic correlation. *Am J Surg Pathol*. 1988; 12(4):251–263.
11. Compagno, J, et al. Microcystic adenomas of the pancreas (glycogen-rich cystadenomas): a clinicopathologic study of 34 cases. *Am J Clin Pathol*. 1978; 69(3):289–298.

Acinar Cell Cystadenoma

KEY FACTS

Terminology

- Benign pancreatic cyst lined by acinar cells

Clinical Issues

- Young to middle-aged
    - Reported range: 16-66 years
- Benign cyst without risk of malignant transformation

Macroscopic

- Unilocular to multilocular thin-walled cyst(s) filled with serous fluid
- Size range: 1.5-10.0 cm

Microscopic

- Cysts lined by single layer of cuboidal epithelium without multilayering
- Budding/incipient acinar structures frequently seen, providing evidence of acinar differentiation

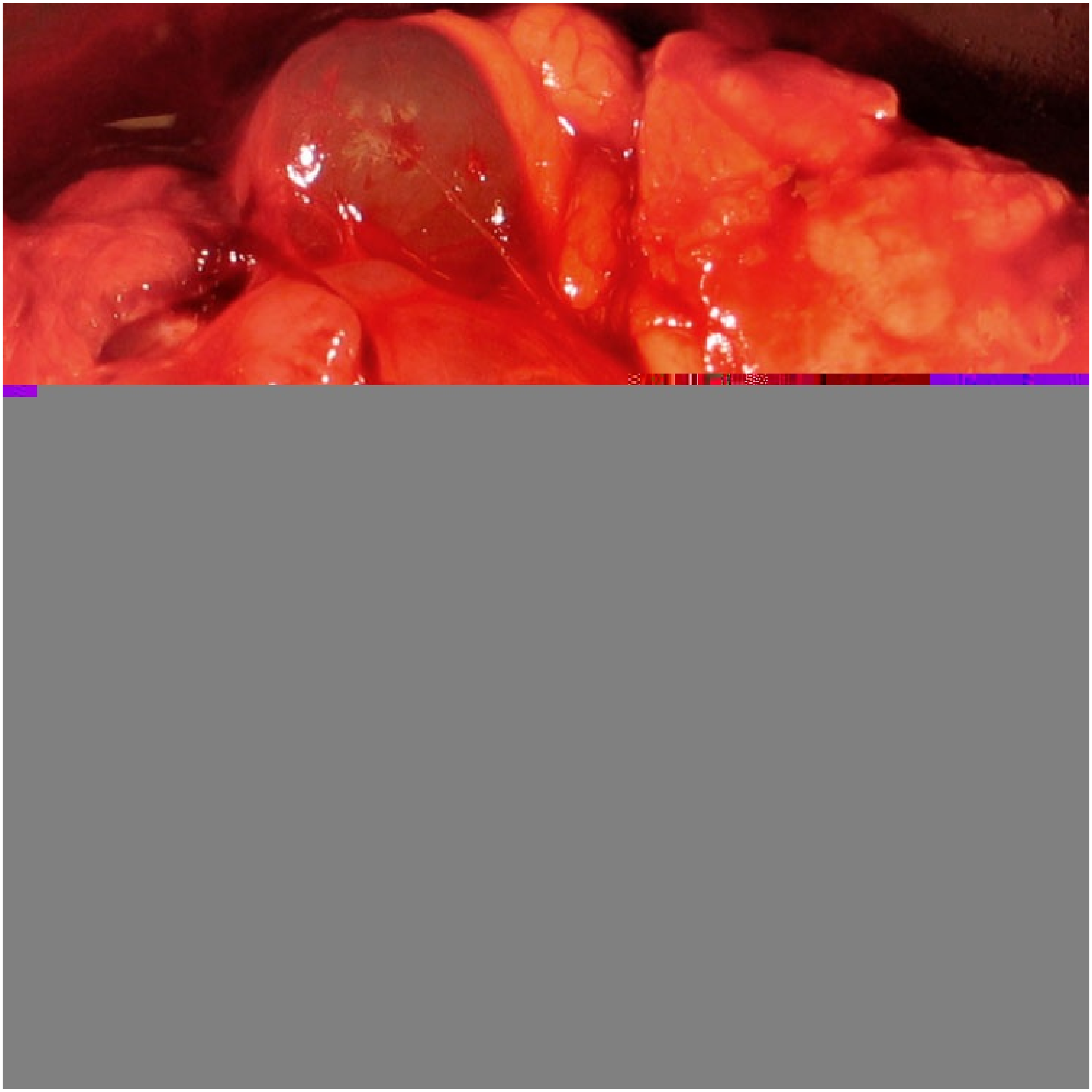
Ancillary Tests

- Lining cells are positive for trypsin &/or lipase

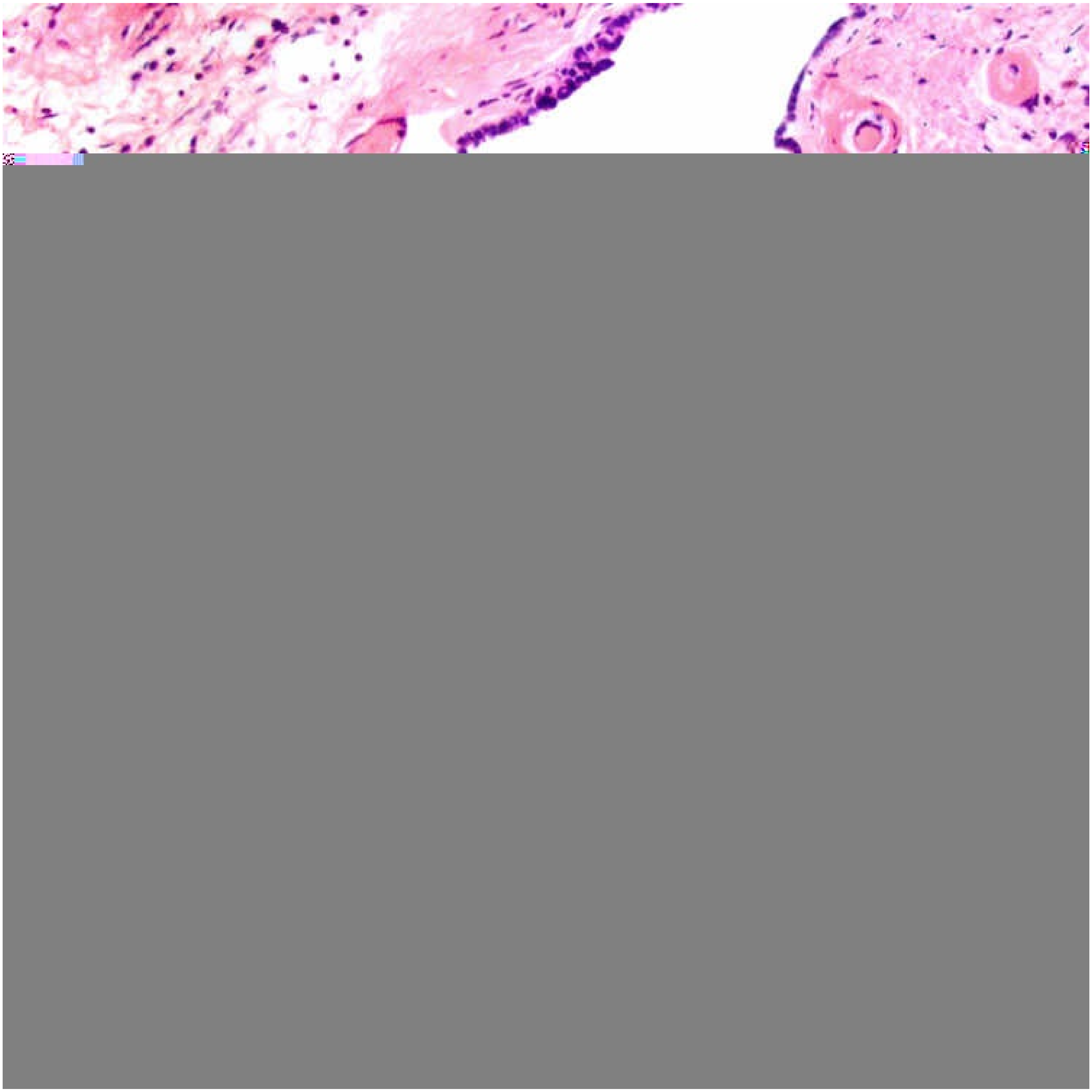
Top Differential Diagnoses

- Serous cystadenoma
    - Also lined by single layer of cuboidal epithelium
- Retention cyst
    - Lacks morphological or immunohistochemical evidence of acinar cell differentiation
- Intraductal papillary-mucinous neoplasm and mucinous cystic neoplasm

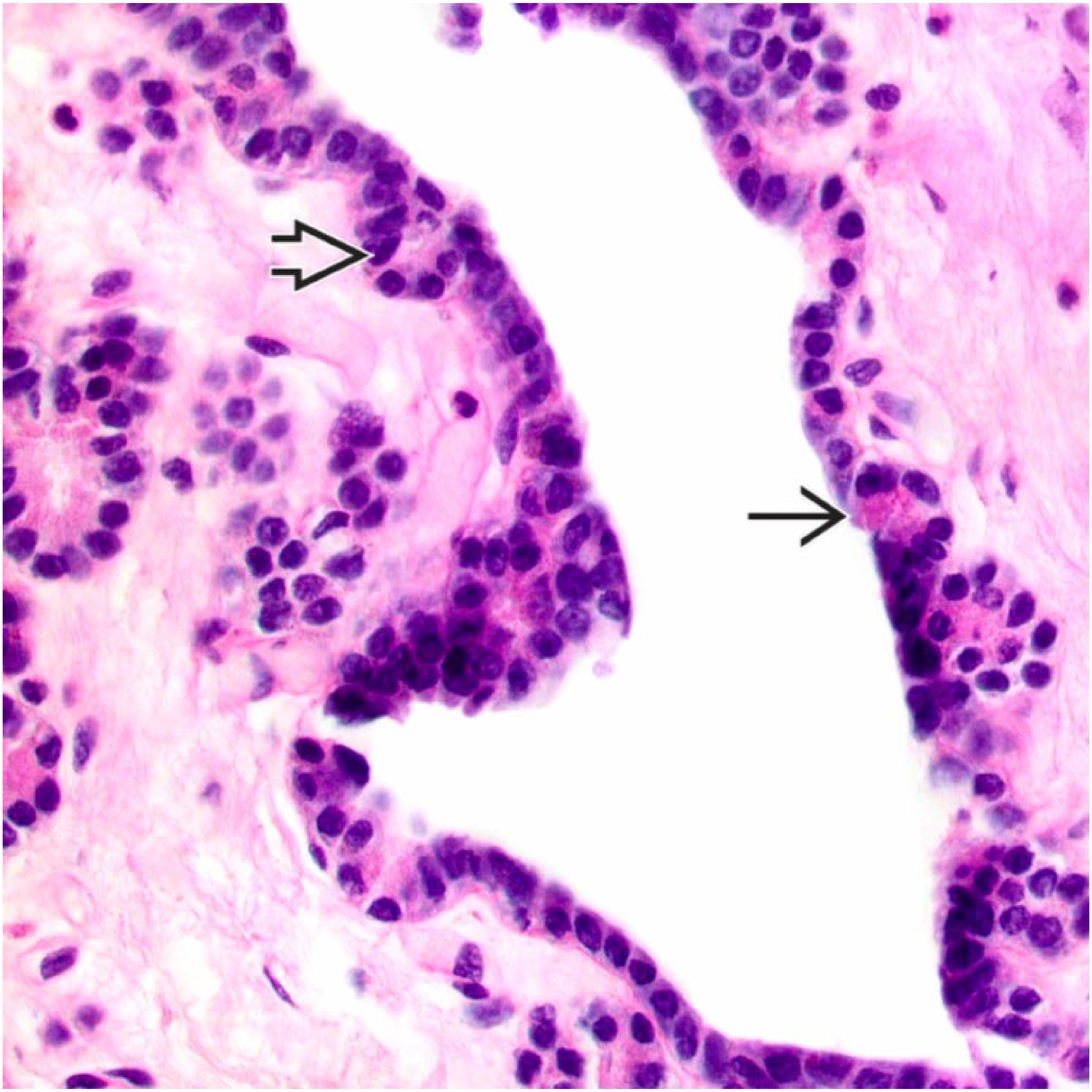
- Neoplastic cysts lined by mucinous epithelium
- Acinar cell cystadenocarcinoma and acinar cell carcinoma
  - Both lesions show sheets of neoplastic cells with nuclear atypia and many mitoses



Gross Photo of Multiple Unilocular Cysts
This acinar cell cystadenoma shows multiple unilocular, thin-walled cysts. The cysts are filled with clear fluid and lack a mural nodule.

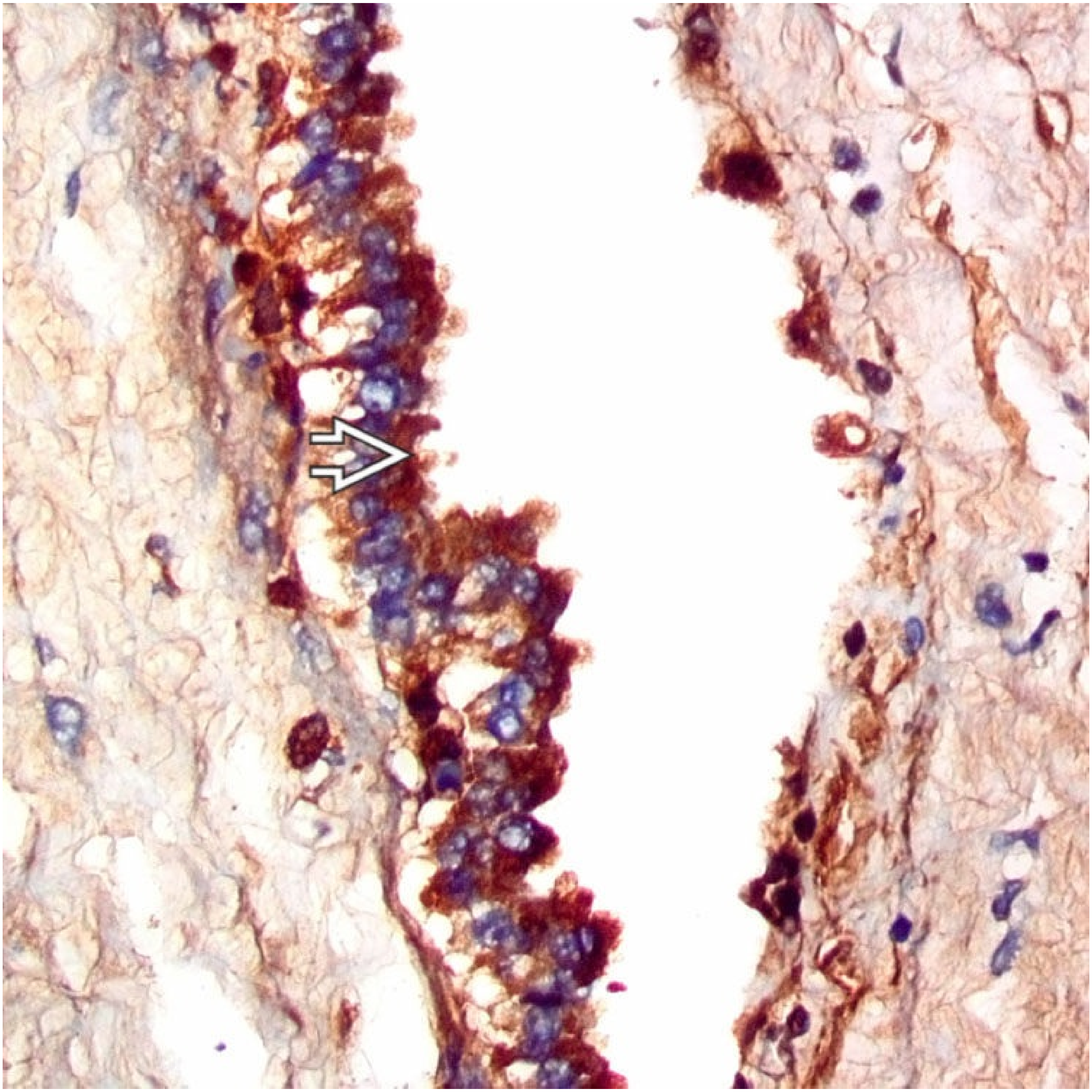


Low Magnification
Acinar cell cystadenomas are lined by a single layer of cuboidal epithelium and could easily be mistaken for a serous cystadenomas.



Higher Magnification

Incipient acinar structures ⇨ are seen on this H&E section. Some of the cells lining these structures show apical eosinophilic granules →. These granules are PAS positive and diastase resistant and represent zymogen granules.


Immunohistochemical Stain for Trypsin
The apical cytoplasmic compartment of the cyst lining cells is positive for trypsin.

TERMINOLOGY

Definitions

• Benign pancreatic cyst lined by cells with acinar cell differentiation

CLINICAL ISSUES

Epidemiology

- Age
  - Young to middle-aged
    – Reported range: 16-66 years
- Sex
  - More common in women

Presentation

- Abdominal pain
- Incidentally detected by imaging

Natural History

- Benign cyst without risk of malignant transformation

Treatment

- Surgical resection is curative

Prognosis

- Benign tumor with excellent prognosis

IMAGING

General Features

- Unilocular to multilocular cyst without solid areas or papillary projections
- Occasionally multiple cysts could involve entire pancreas

MACROSCOPIC

General Features

- Unilocular to multilocular, thin-walled cyst(s) filled with serous fluid
- No dilatation of main pancreatic duct
- Both pancreatic head and body/tail are involved

Sections to Be Submitted

- Entire cyst should be submitted for histological evaluation

Size

- Range: 1.5-10.0 cm
- Incidentally detected cysts identified during pathologic examination may measure < 1 cm

MICROSCOPIC

Histologic Features

- Cyst lined by single layer of cuboidal epithelium without multilayering or pseudostratification
  - In areas, lining epithelium may be flattened and resemble ductal epithelium
- Budding/incipient acinar structures frequently seen, providing evidence of acinar differentiation
  - Smaller acinar structures may surround dominant cyst
  - Apical cytoplasmic compartment shows deeply eosinophilic granules
- Eosinophilic intraluminal concretions are frequently seen
- Bland, basally placed nuclei with small nucleoli
- Mitoses are absent

ANCILLARY TESTS

Histochemistry

- PAS-D
  - Reactivity: Positive
  - Staining pattern: Apical cytoplasmic compartment

Immunohistochemistry

- Lining cells are focally positive for trypsin &/or lipase
- Cells are positive for CAM5.2 and negative for chromogranin and synaptophysin

Electron Microscopy

- Cyst lining cells show apical, round, electron-dense granules measuring 200-800 nm that resemble normal pancreatic zymogen granules

DIFFERENTIAL DIAGNOSIS

Serous Cystadenoma

- Also lined by single layer of cuboidal epithelium
  - Cytoplasm of lining cells is clear and filled with glycogen
- On PAS-D stain, cells of serous cystadenoma lack intracellular granules, and apical PAS-D granules are seen in acinar cell cystadenomas
- Lacks incipient acinar structures, and on immunohistochemistry, cells are negative for trypsin

Retention Cyst

- Lacks morphological or immunohistochemical evidence of acinar cell differentiation

Intraductal Papillary-Mucinous Neoplasm and Mucinous Cystic Neoplasm

- Neoplastic cysts lined by mucinous epithelium
    - Mucinous lining epithelium excludes diagnosis of acinar cell cystadenoma

Acinar Cell Cystadenocarcinoma and Acinar Cell Carcinoma

- Both lesions show sheets of neoplastic cells with nuclear atypia and many mitoses

SELECTED REFERENCES

1. Delavaud, C, et al. CT and MR imaging of multilocular acinar cell cystadenoma: comparison with branch duct intraductal papillary mucinous neoplasia (IPMNs). *Eur Radiol*. 2014; 24(9):2128–2136.
2. Singhi, AD, et al. Acinar cell cystadenoma of the pancreas: a benign neoplasm or non-neoplastic ballooning of acinar and ductal epithelium? *Am J Surg Pathol*. 2013; 37(9):1329–1335.
3. Khor, TS, et al. Acinar cystadenoma of the pancreas: a clinicopathologic study of 10 cases including multilocular lesions with mural nodules. *Am J Surg Pathol*. 2012; 36(11):1579–1591.
4. Albores-Saavedra, J. Acinar cystadenoma of the pancreas: a previously undescribed tumor. *Ann Diagn Pathol*. 2002; 6(2):113–115.
5. Chatelain, D, et al. Unilocular acinar cell cystadenoma of the pancreas an unusual acinar cell tumor. *Am J Clin Pathol*. 2002; 118(2):211–214.
6. Couvelard, A, et al. [Acinar cystic transformation of the pancreas (or acinar cell cystadenoma), a rare and recently described entity.]. *Ann Pathol*. 2002; 22(5):397–400.
7. Zamboni, G, et al. Acinar cell cystadenoma of the pancreas: a new entity? *Am J Surg Pathol*. 2002; 26(6):698–704.

Mucinous Cystic Neoplasm

KEY FACTS

Terminology

- Neoplasm composed of mucin-producing epithelial cells associated with ovarian-type stroma

Clinical Issues

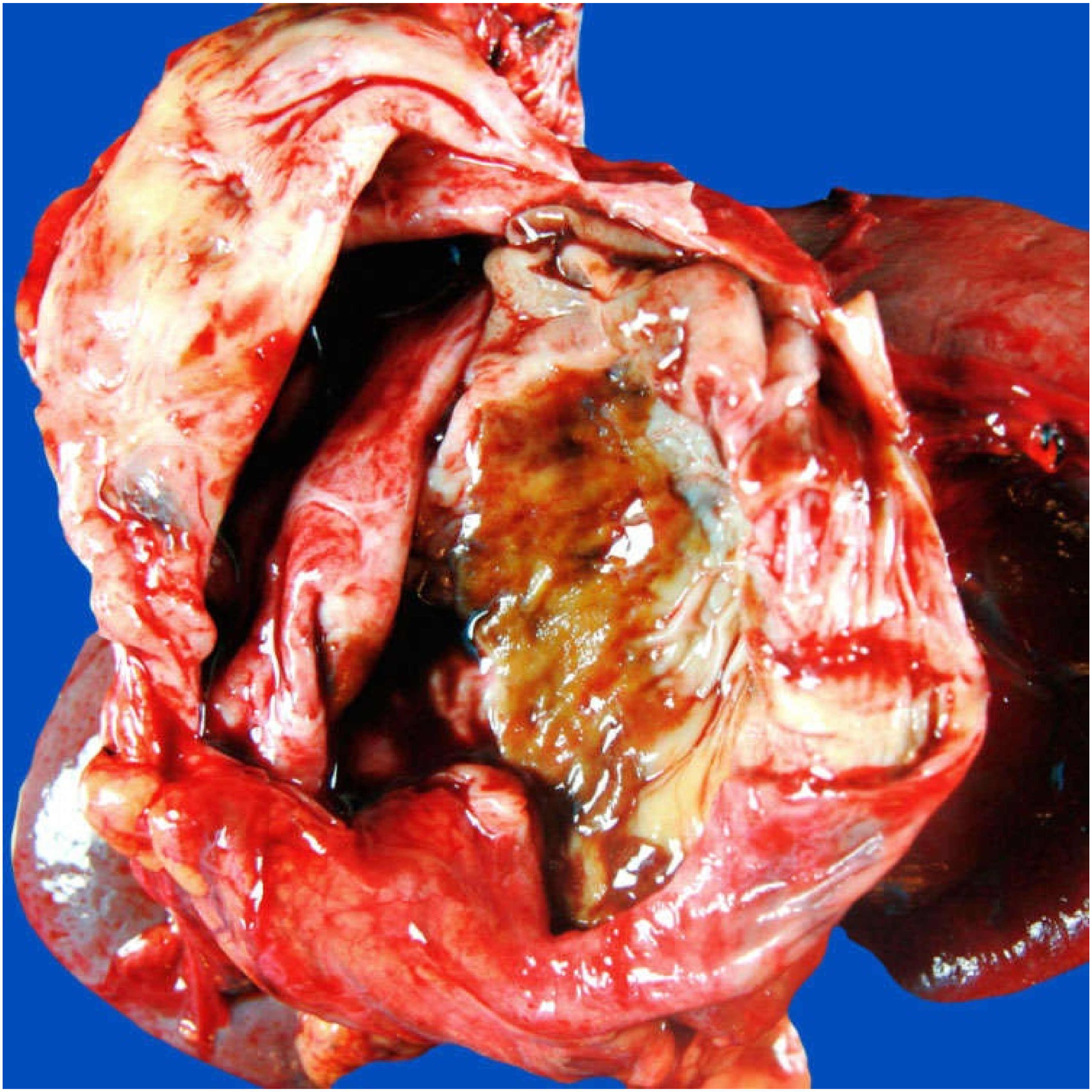
- Comprises 10% of cystic lesions of pancreas
  - Average age at diagnosis: 40-50 years
  - Range: 14-95 years
- Predominantly female
  - F:M = 20:1

Macroscopic

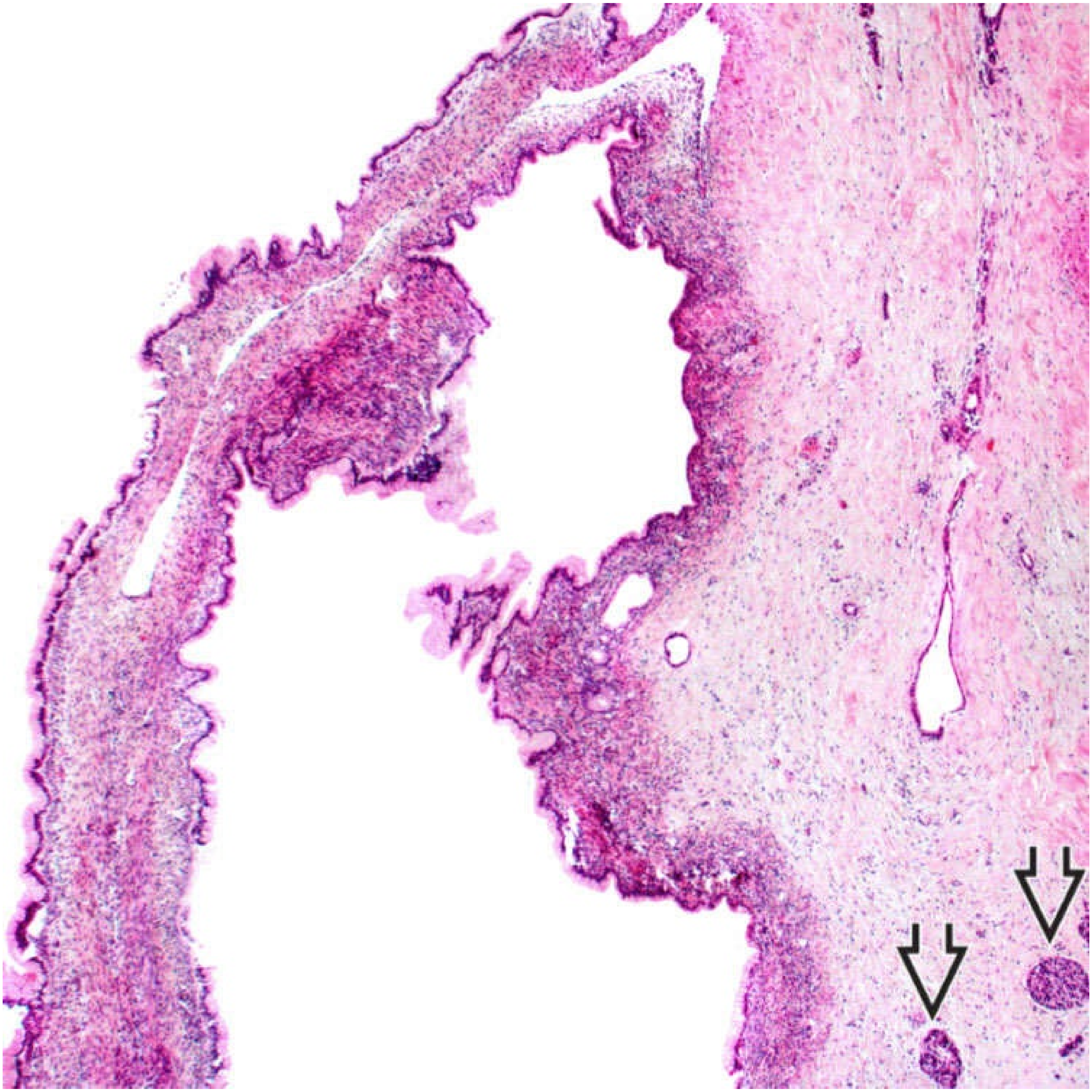
- 90% of mucinous cystic neoplasms arise in body or tail of pancreas
  - Usually solitary and large
  - Mean: 7-10 cm
- Usually multiloculated with thick walls; filled with thick, tenacious mucoid material

Microscopic

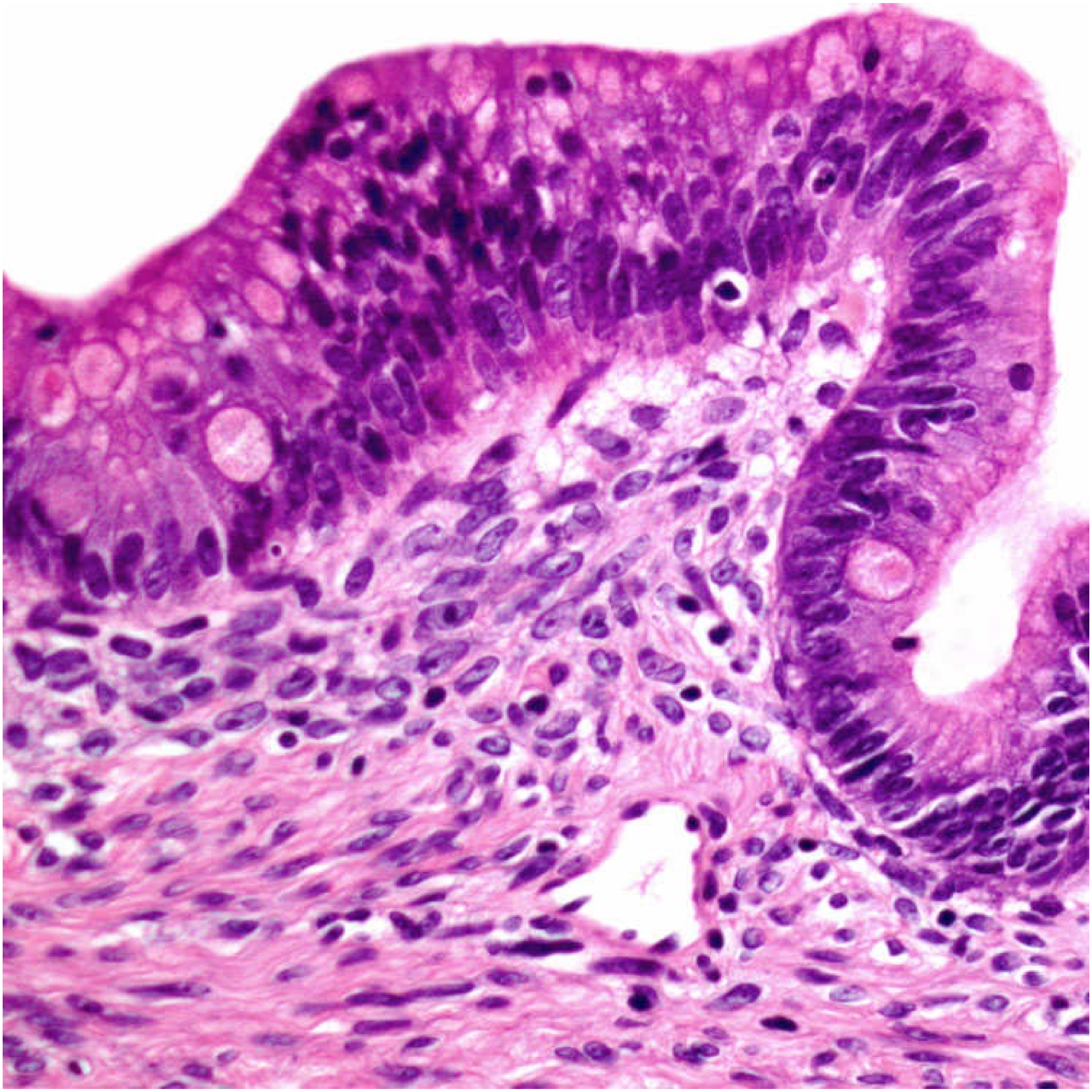
- Tall, columnar, mucin-producing epithelium with varying degrees of cellular atypia
  - Invasive components can be very focal
  - Recommended to submit entire lesion for microscopic evaluation
- Ovarian-type stroma is required for diagnosis
  - Broad areas of stroma may be hyalinized
- Low- and high-grade dysplasia depending on degree of cytologic atypia
- Invasive carcinoma, usually pancreaticobiliary type, is present in 15% of cases



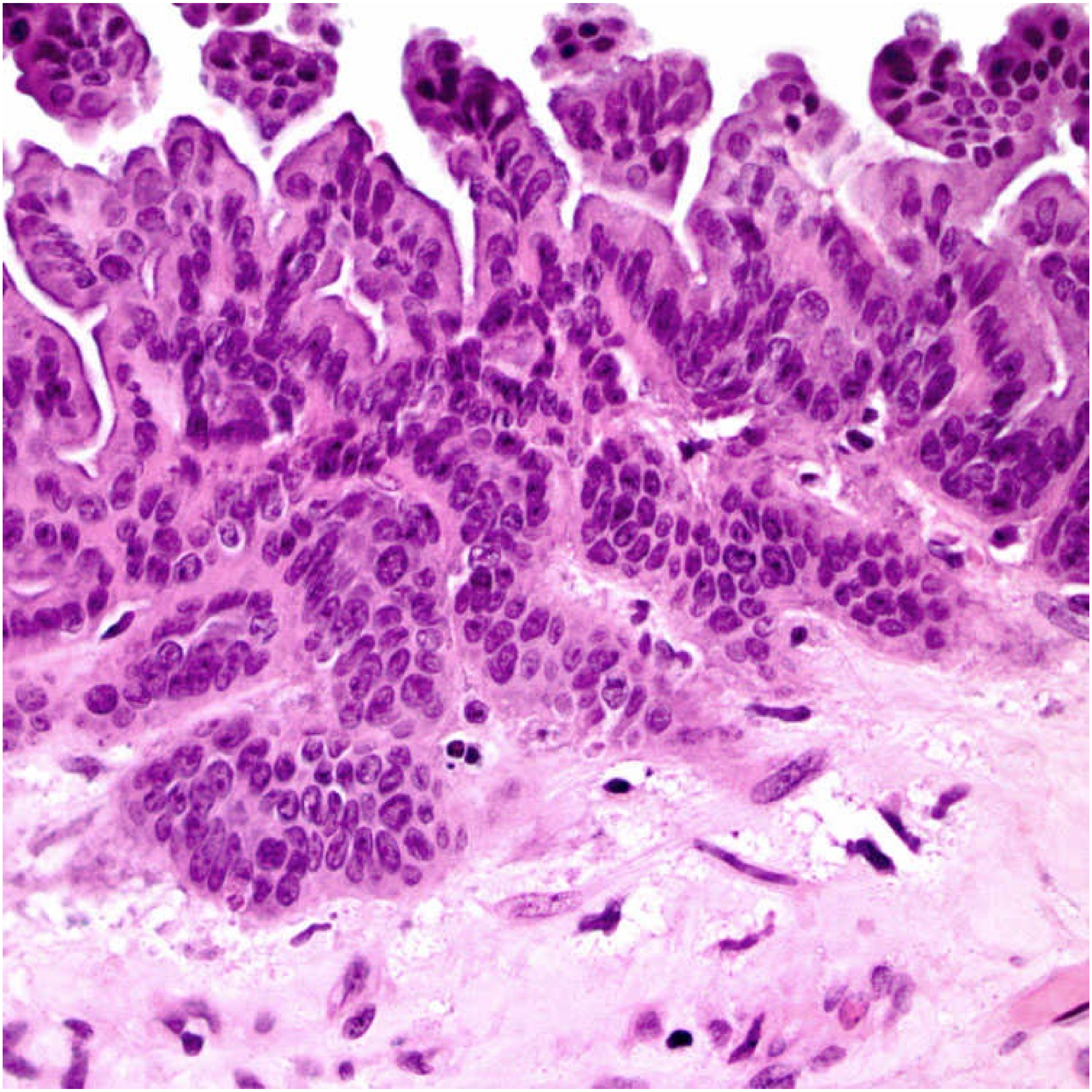
Mucinous Cystic Neoplasm
Unilocular cyst with a smooth, partially discolored lining is shown located in the tail of the pancreas.



Low-Grade Dysplasia
Cyst lined by tall, columnar mucinous cells with underlying ovarian-type stroma is shown. The adjacent pancreatic parenchyma is fibrotic with a few residual islets ➭ .



Intermediate-Grade Dysplasia
The lining epithelium shows enlarged, hyperchromatic nuclei with crowding and stratification.



High-Grade Dysplasia
The lining epithelium shows papillary to micropapillary architecture and high-grade cytologic atypia.

TERMINOLOGY

Abbreviations

- Mucinous cystic neoplasm (MCN)

Definitions

- Neoplasm composed of mucin-producing epithelial cells associated with ovarian-type stroma

ETIOLOGY/PATHOGENESIS

Molecular Changes

- *KRAS2* mutation is seen in 20% of low-grade, 33% of intermediate-grade, and 90% of high-grade MCNs
- *TP53* mutation and DPC4/SMAD4 loss usually seen only in advanced MCN, in invasive component

Proposed Pathogenesis

- Ovarian-type stroma may develop from endodermal immature stroma stimulated by female hormones
- May develop from primary yolk cells implanted in pancreas during embryogenesis

CLINICAL ISSUES

Epidemiology

- Incidence
  - 10% of cystic lesions in pancreas
- Age
  - Range: 14-95 years (average at diagnosis: 40-50)
- Sex
  - Predominantly female (F:M = 20:1)

Presentation

- Vague abdominal symptoms (pain and fullness) with compression of adjacent organs and tissues

Prognosis

- Excellent prognosis for patients with MCN without invasion
  - 5-year survival rate of 50% for invasive MCN
  - Size and extent of invasion (confined to pancreas vs. beyond tumor capsule) and age of patient (lower survival rate > 50 years) correlates with survival

IMAGING

CT Findings

- Usually large, well-demarcated, thick-walled, multilocular cystic mass with peripheral calcification (20%)
- Mural nodules and papillary excrescences are more common in MCN with invasive component

ERCP Findings

- Main pancreatic duct and large interlobular ducts do not communicate with cysts in majority of cases

MACROSCOPIC

General Features

- 90% in body or tail of pancreas
- Usually solitary and large (mean: 7-10 cm)
- Usually multiloculated with thick walls; filled with thick, tenacious mucoid material
- Intracystic papillary excrescences &/or mural nodules suggestive of high-grade dysplasia or invasion

MICROSCOPIC

Histologic Features

- Usually surrounded by thick band of heavily collagenized tissue that separates cysts from adjacent nonneoplastic pancreatic parenchyma
  - Ovarian-type stroma is required for diagnosis of MCN
  - ○ May be replaced by broad zones of hyalinization; multiple sections may be required to demonstrate cellular stroma
  - ○ Stroma often expresses ER &/or PR
  - – Supporting role of female hormones in its pathogenesis

○ Inhibin expression seen in ovarian stroma

- Lined (at least focally) by tall, columnar, mucin-producing epithelium
  - ○ Epithelium is often focally denuded; several histologic sections may be needed to demonstrate epithelial lining
  - ○ May be focally lined by flat &/or cuboidal cells of pancreatobiliary type
  - ○ Varying degrees of cellular atypia
    - – Low-grade dysplasia
    - – High-grade dysplasia (carcinoma-in-situ)
- Invasive carcinoma is present in 15% of MCNs
  - ○ Large size (> 5 cm) and intracystic mural nodules > 1 cm are associated with invasive component
  - ○ Most are adenocarcinomas of pancreaticobiliary type

DIFFERENTIAL DIAGNOSIS

Pseudocyst

- More common in men than women; associated with pancreatitis and elevated serum amylase levels

Intraductal Papillary Mucinous Neoplasms

- More common in men than women
- Often demonstrate communication with pancreatic duct system and lack ovarian-type stroma
- Present in head of gland more frequently than body/tail

Serous Cystic Neoplasm

- Smaller cysts, central stellate scar, and glycogen-rich cuboidal lining cells

Solid-Pseudopapillary Neoplasm

- Areas of necrosis and hemorrhage associated with dropout of dyshesive tumor cells

DIAGNOSTIC CHECKLIST

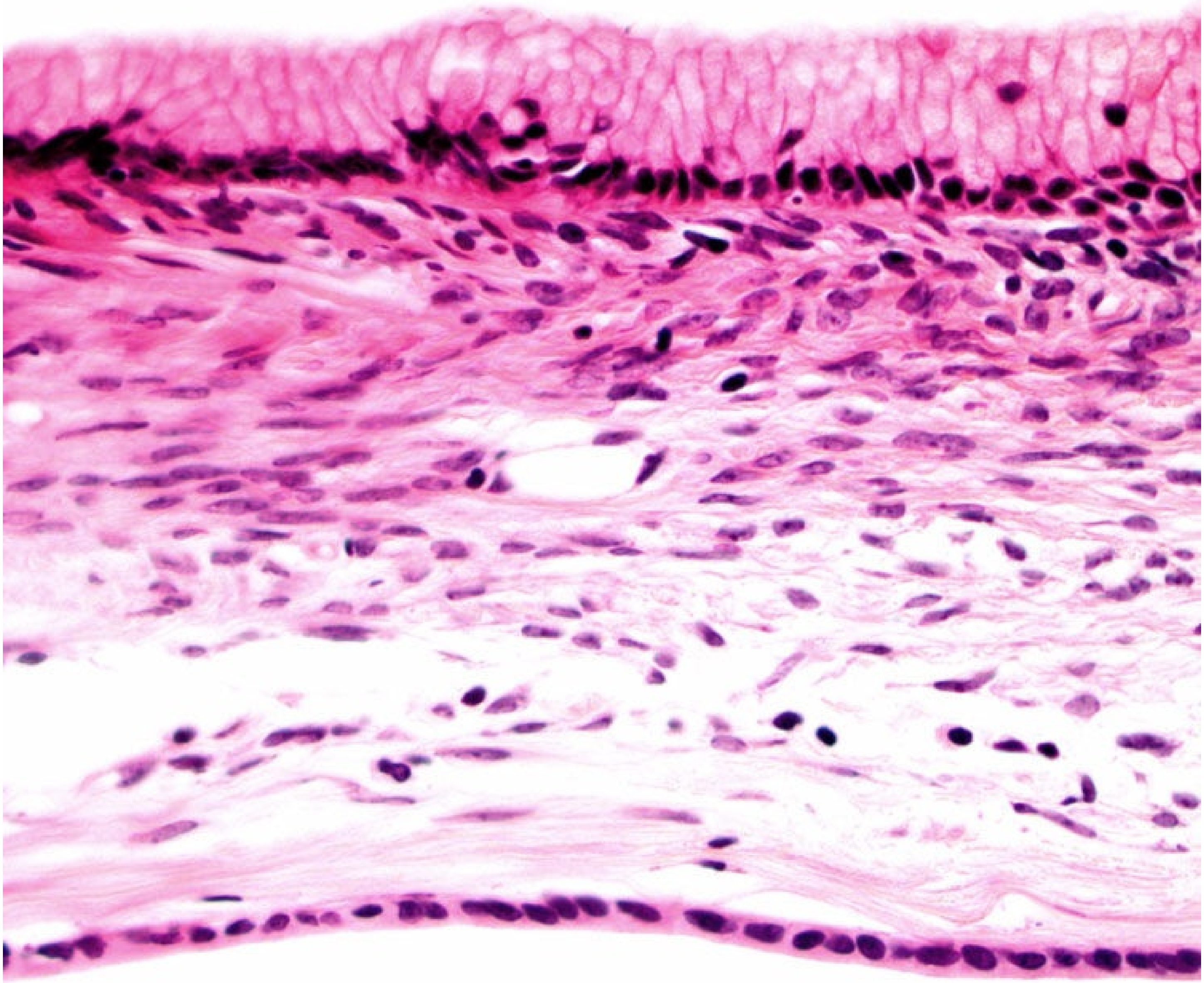
Clinically Relevant Pathologic Features

- Presence or absence of invasive carcinoma is best predictor of survival following surgical resection
- Invasive components can be very focal, thus submission of entire neoplasm is recommended
- Staging of mucinous cystic neoplasms with associated invasive carcinoma follows same staging system applied to carcinomas of exocrine pancreas

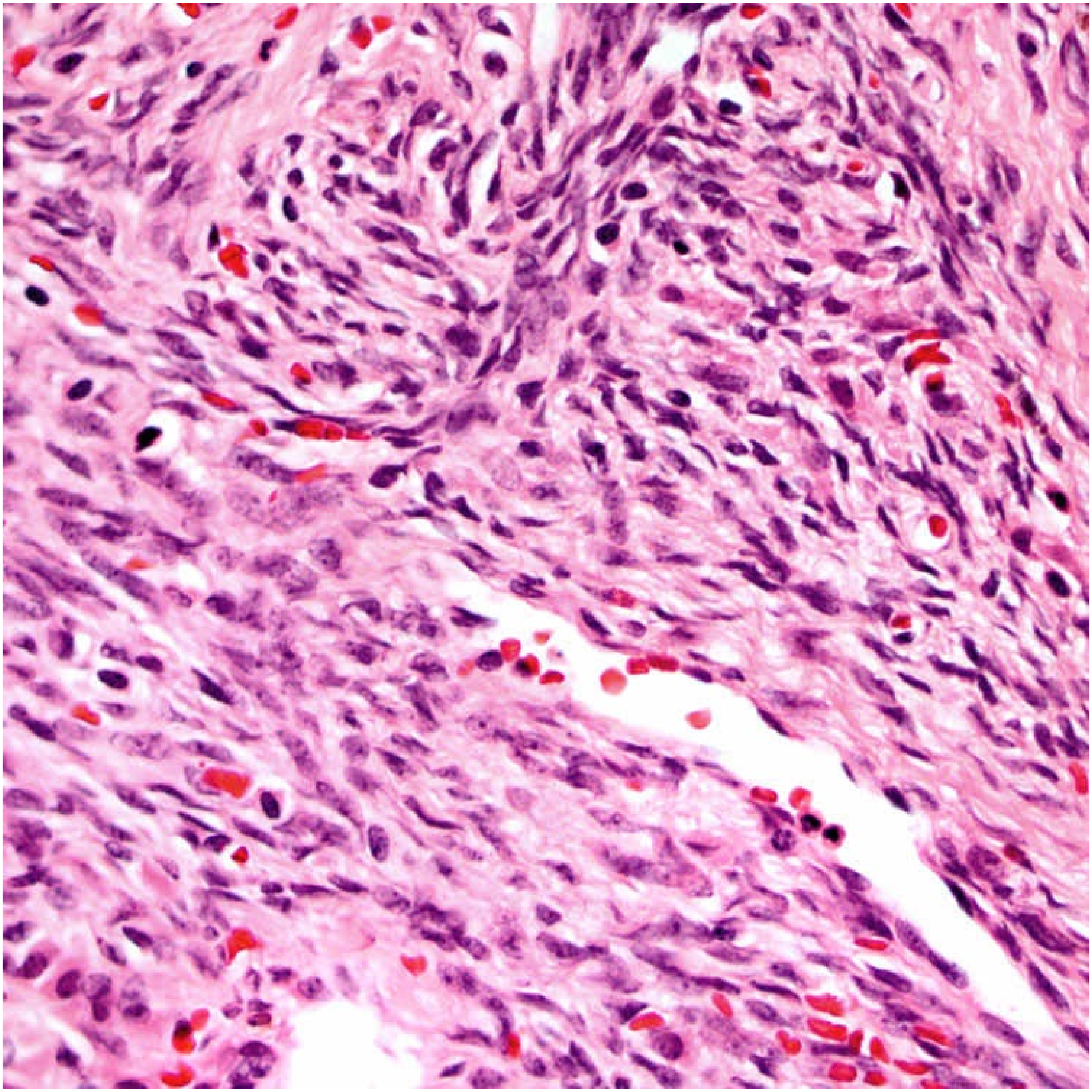
Pathologic Interpretation Pearls

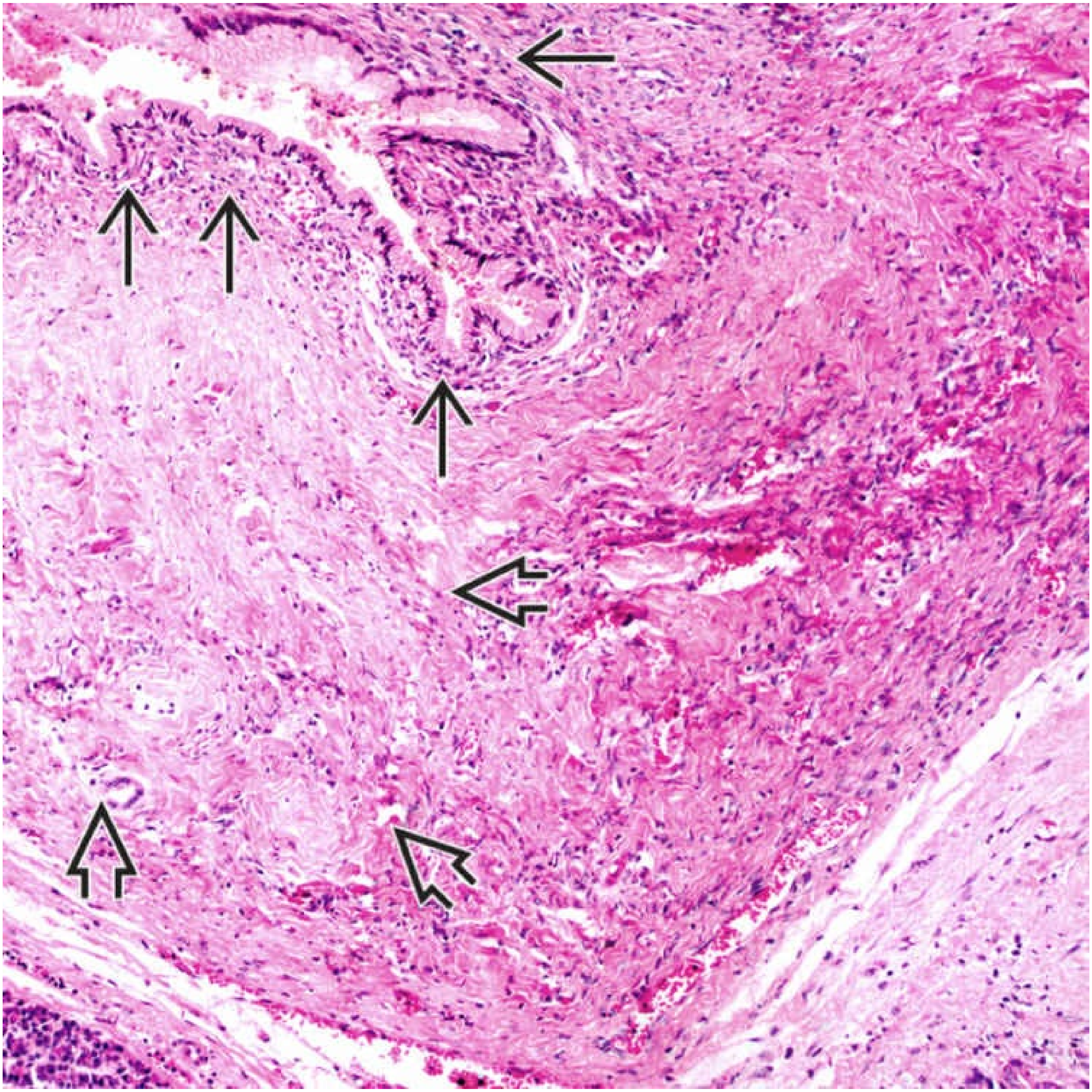
- Ovarian-type stroma required for diagnosis of MCN

Mucinous Cystic Neoplasm
Thick, fibrous wall is shown with ovarian-type stroma located underneath the epithelial lining → and extending into the periductal regions ⇨ .

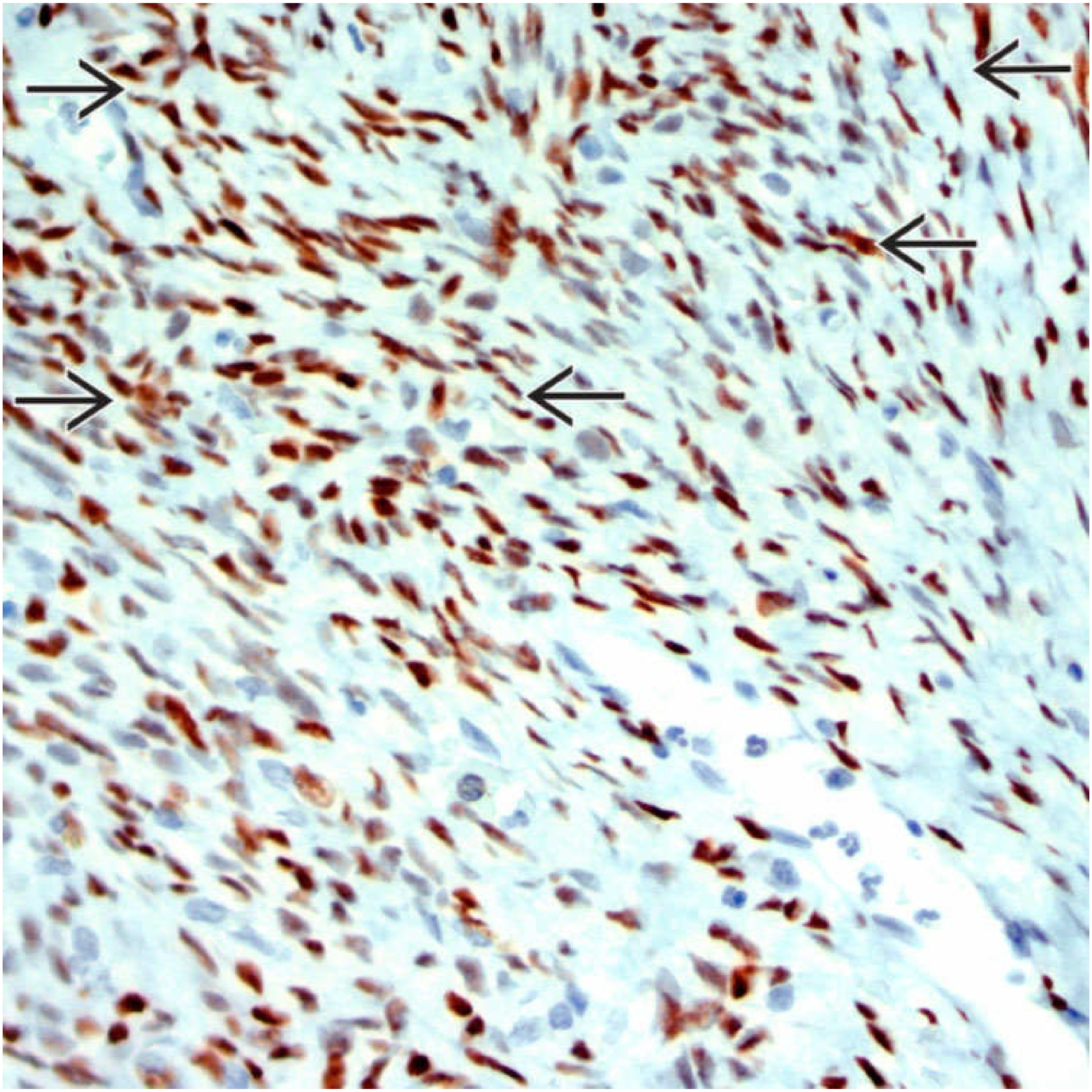


Low-Grade Dysplasia
Epithelium with low-grade dysplasia can consist of flat, cuboidal, or mucinous columnar epithelial cells without significant atypia.

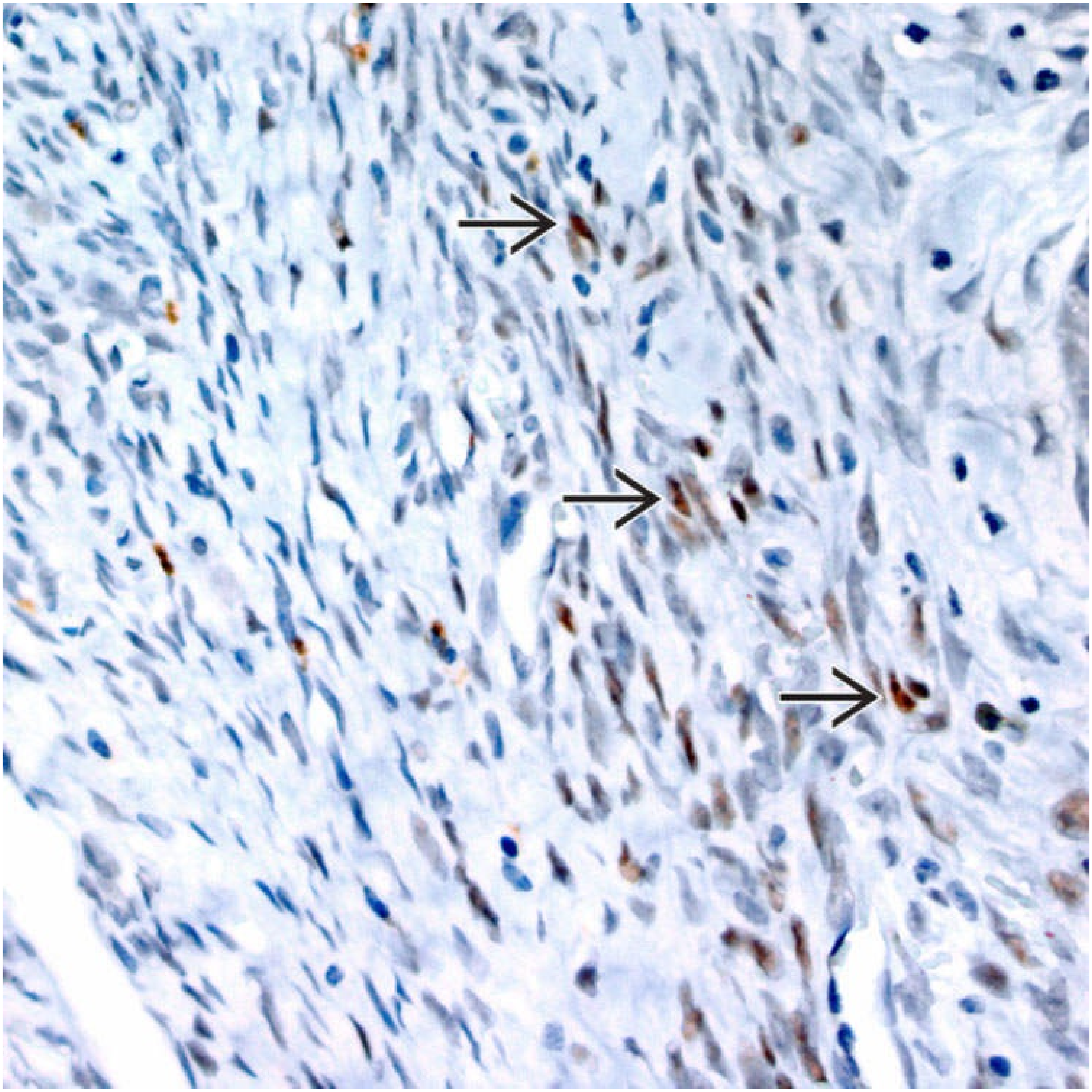

Ovarian-Type Stroma
Ovarian-type stroma consists of densely packed spindle cells with scant cytoplasm and uniform, elongated, wavy nuclei. Mitoses are rare to absent.



Stromal Cells
Some mucinous cystic neoplasms have markedly hyalinized stroma ➪ and scant ovarian-type stroma →.
Multiple sections may be required to demonstrate the ovarian-type stroma required for diagnosis.

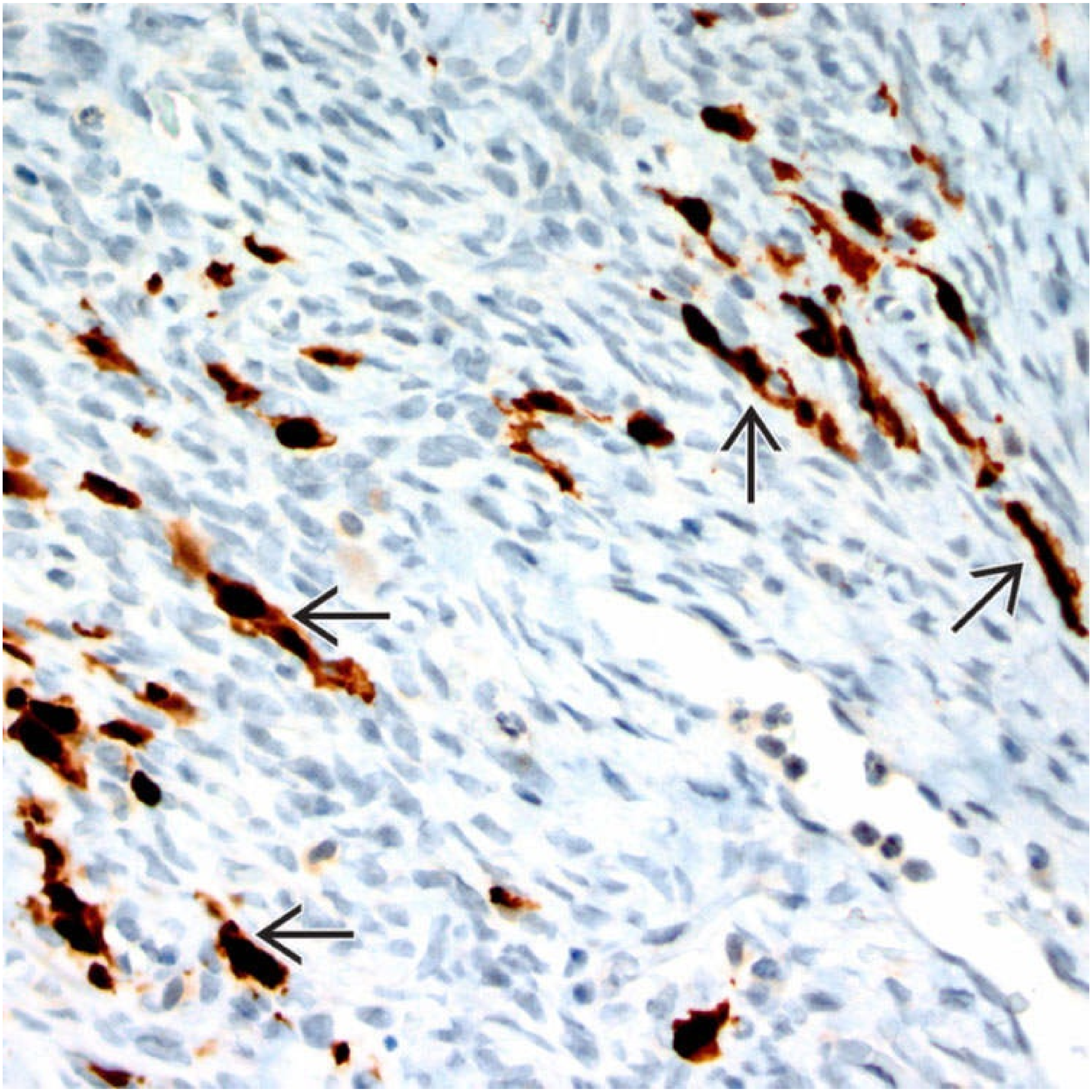


Ovarian-Type Stroma
Some subepithelial spindle cells are reactive to an antibody against progesterone receptor → in 50-75% of mucinous cystic neoplasms.



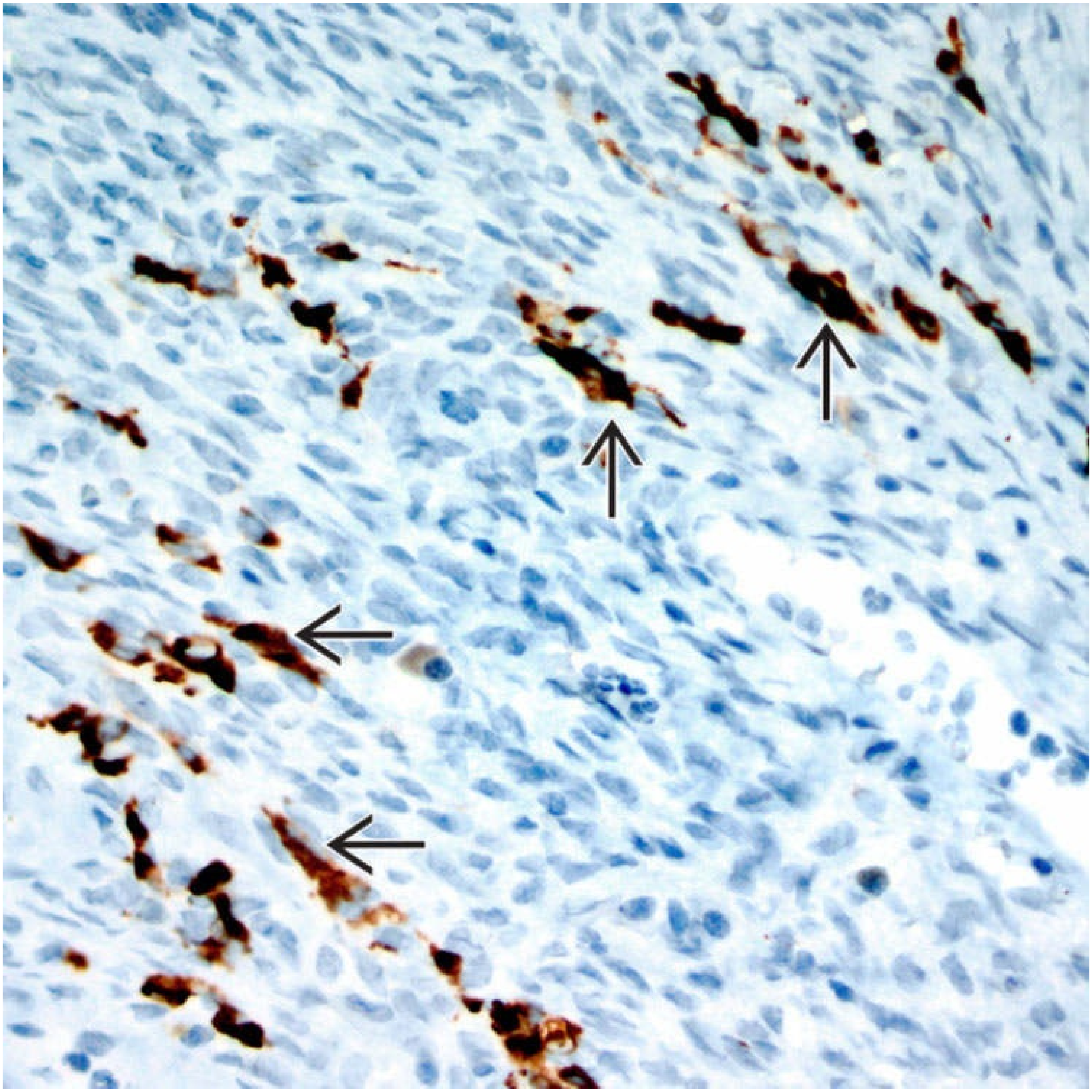
Ovarian-Type Stroma

Estrogen receptors are expressed in subepithelial spindle cells → in 25% of mucinous cystic neoplasms, less extensively than progesterone receptor. These spindle cells also label with antibodies to vimentin, smooth muscle actin, desmin, CD99, and Bcl-2; this immunophenotype is strikingly similar to that of normal ovarian stroma.



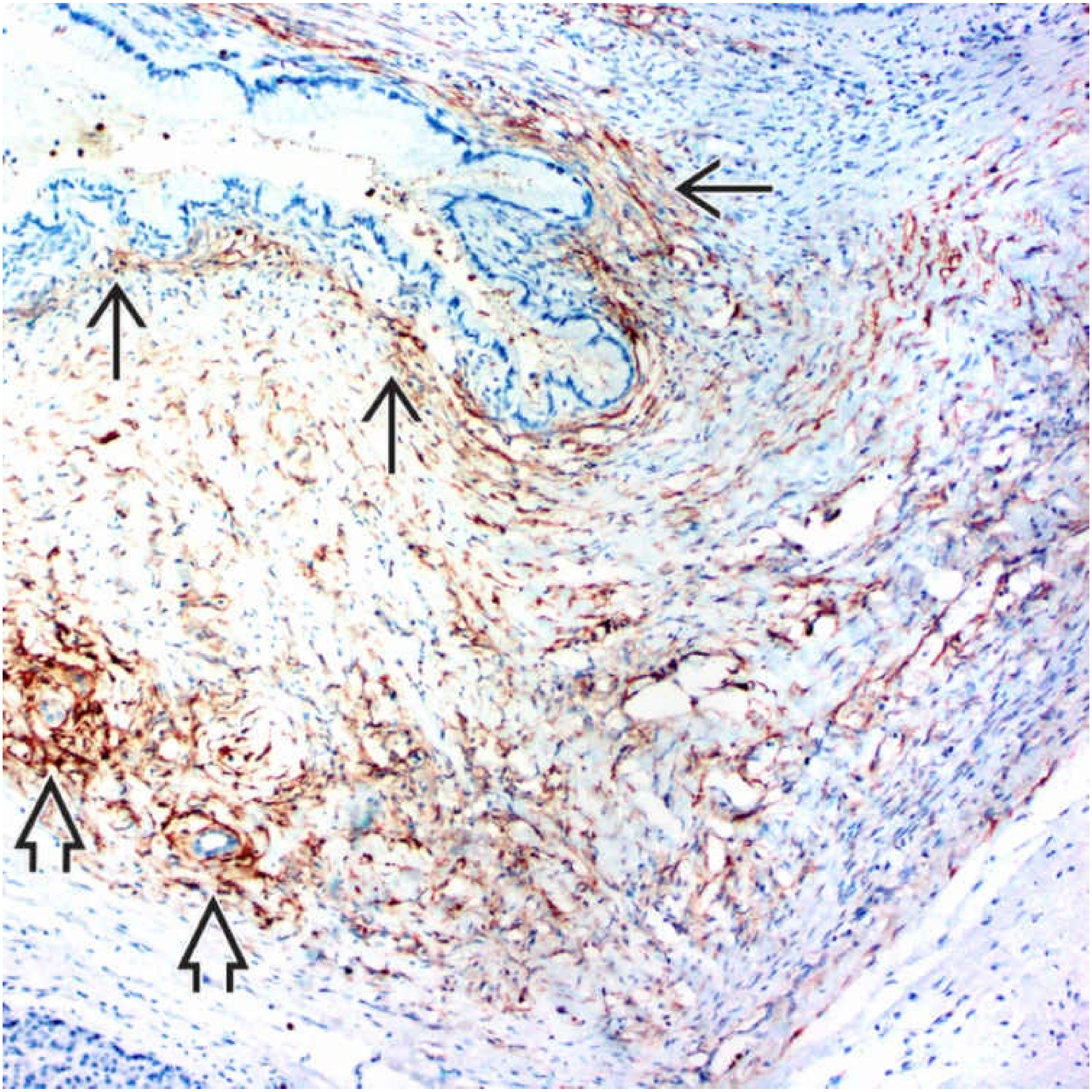
Ovarian-Type Stroma

The luteinized cells also label with an antibody to calretinin → along with tyrosine hydroxylase and Melan-A, markers that are reactive to normal hilar cells of the ovary. S100 and CD34 are usually negative.



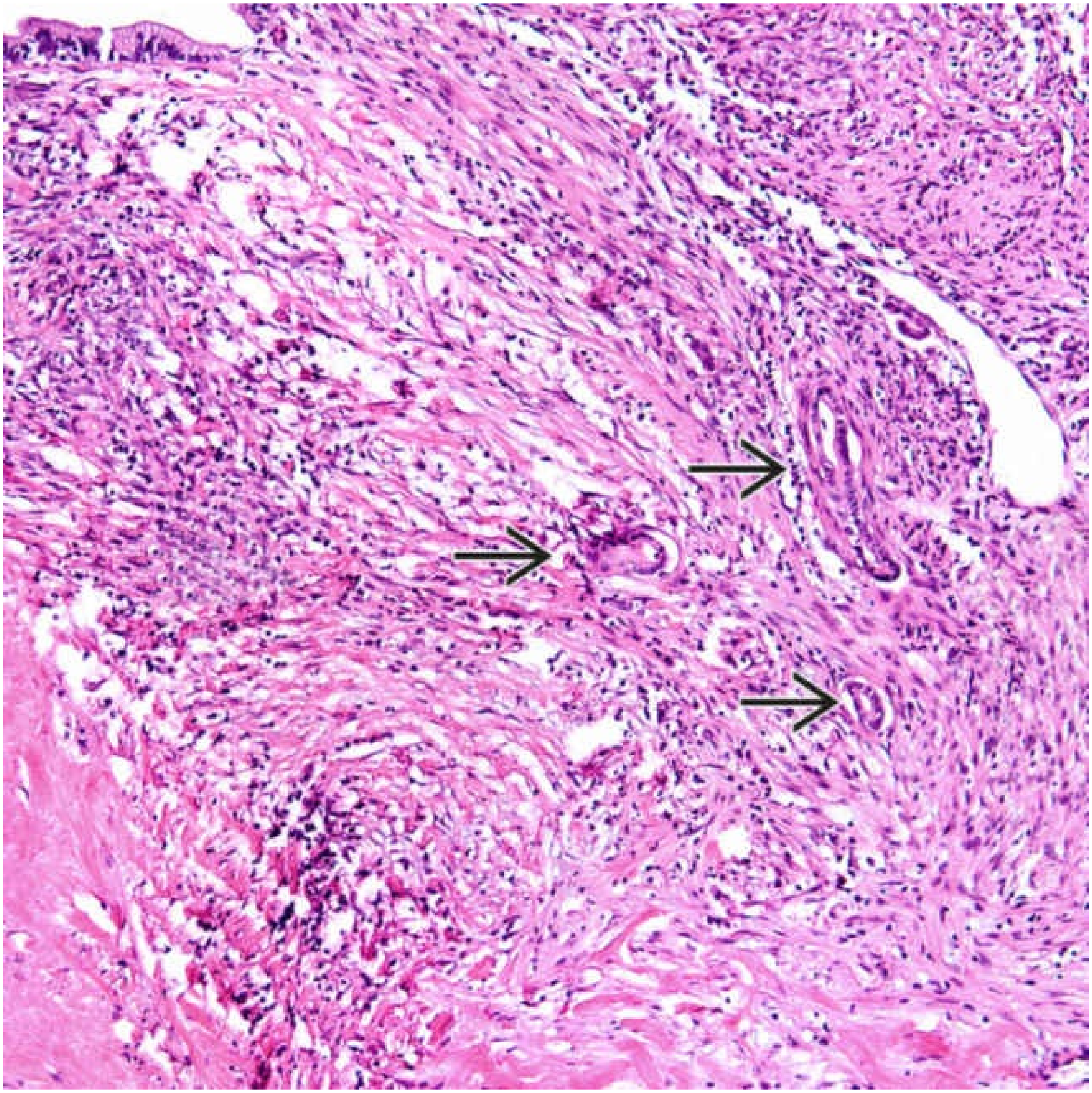
Ovarian-Type Stroma

The luteinized cells of the ovarian-type stromal cells label with an antibody to inhibin-α →.



Stromal Cells

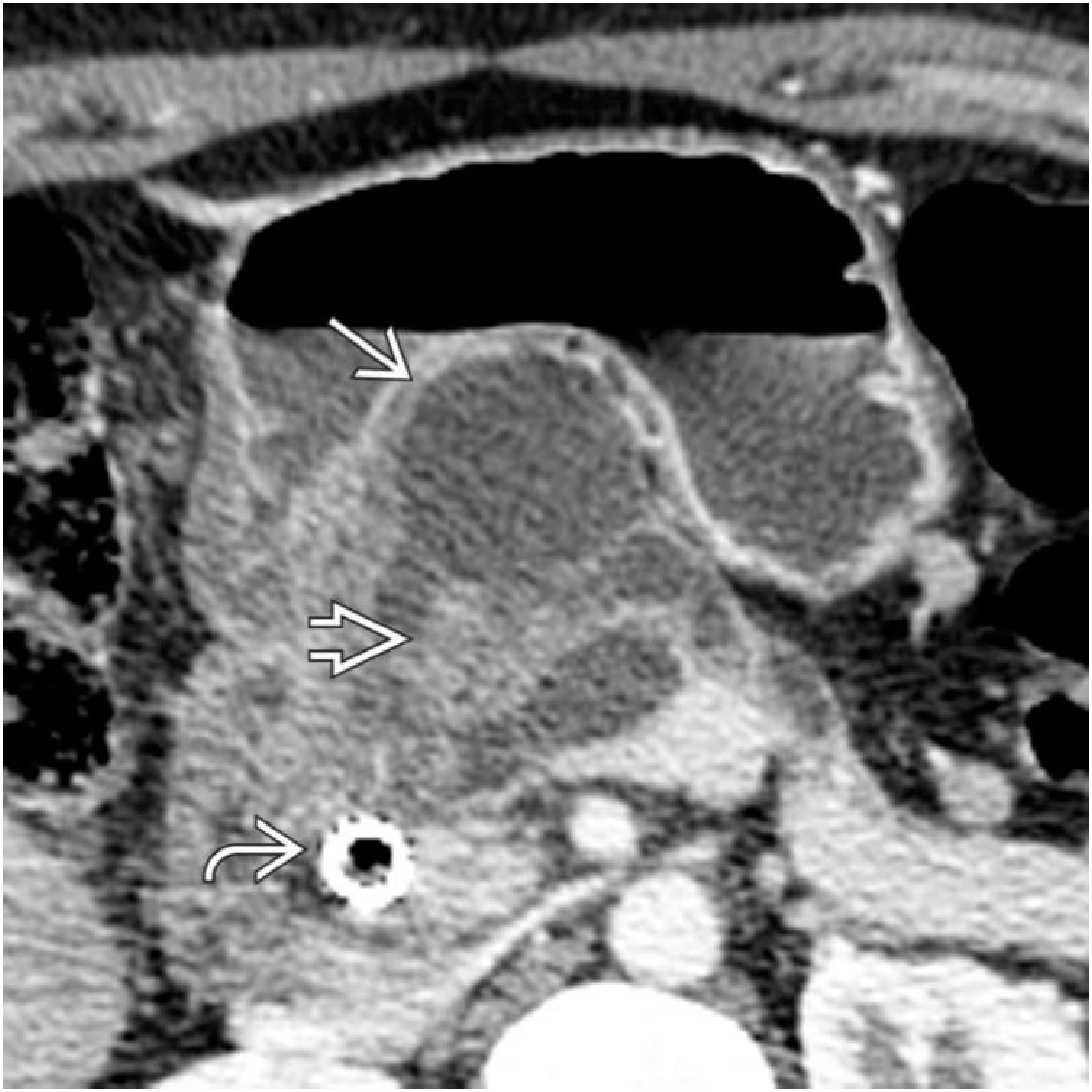
The hyalinized stroma is reactive to an antibody against CD10 ⇨ with some accentuation in the subepithelial region →. When the ovarian-type stroma is indiscernible, CD10 expression may suggest the possibility of its hyalinization.



Focal Invasion
Adenocarcinoma with focal invasion arising in MCN features a few infiltrating malignant glands → within the ovarian-type stroma.

MR Appearance

MR shows a well-defined cystic mass ⇒ in the pancreatic tail. Note the enhancing wall and septa. The individual cysts within the mass are few and relatively large (~ 2 cm in diameter).



CECT Appearance
CECT shows a large, complex cystic pancreatic body mass with internally enhancing soft tissue. The mass resulted in biliary obstruction and required placement of a metallic stent. The presence of enhancing soft tissue within a cystic mass makes carcinoma the leading diagnostic possibility.

SELECTED REFERENCES

1. Basturk, O, et al. A revised classification system and recommendations from the Baltimore consensus meeting for neoplastic precursor lesions in the pancreas. *Am J Surg Pathol*. 2015; 39(12):1730–1741.
2. Jang, KT, et al. Clinicopathologic characteristics of 29 invasive carcinomas arising in 178 pancreatic mucinous cystic neoplasms with ovarian-type stroma: implications for management and prognosis. *Am J Surg Pathol*. 2015; 39(2):179–187.

3.Nishigami, T, et al. Comparison between mucinous cystic neoplasm and intraductal papillary mucinous neoplasm of the branch duct type of the pancreas with respect to expression of CD10 and cytokeratin 20. *Pancreas*. 2009; 38(5):558–564.
4.Crippa, S, et al. Mucinous cystic neoplasm of the pancreas is not an aggressive entity: lessons from 163 resected patients. *Ann Surg*. 2008; 247(4):571–579.
5.Wilentz, RE, et al. Mucinous cystic neoplasms of the pancreas. *Semin Diagn Pathol*. 2000; 17(1):31–42.
6.Thompson, LD, et al. Mucinous cystic neoplasm (mucinous cystadenocarcinoma of low-grade malignant potential) of the pancreas: a clinicopathologic study of 130 cases. *Am J Surg Pathol*. 1999; 23(1):1–16.
7.Wilentz, RE, et al. Pathologic examination accurately predicts prognosis in mucinous cystic neoplasms of the pancreas. *Am J Surg Pathol*. 1999; 23(11):1320–1327.
8.Shyr, YM, et al. Mucin-producing neoplasms of the pancreas. Intraductal papillary and mucinous cystic neoplasms. *Ann Surg*. 1996; 223(2):141–146.

Intraductal Papillary Mucinous Neoplasm

KEY FACTS

Terminology

- Grossly visible, mucin-producing epithelial neoplasm present within main pancreatic duct &/or its branches
  - Classified as main duct, combined, or branch duct type

Clinical Issues

- 20-50% of resected cystic pancreatic tumors
  - Incidence increasing due to increased incidental detection on imaging for other reasons
- Most patients are asymptomatic
  - Symptoms associated with intermittent pancreatic ductal obstruction by tenacious mucin &/or low-grade pancreatitis
- Average age at presentation: Mid 60s
- Prognosis better than conventional ductal adenocarcinoma
  - Noninvasive tumors: 5-year survival rate: > 75%
  - Invasive tumors: 5-year survival rate: 34-62%
    - Significantly better than pancreatic ductal adenocarcinoma
  - Invasive components may be very focal, requiring submission of entire lesion
- Surgical resection treatment of choice
  - Vast majority surgically resectable

Macroscopic

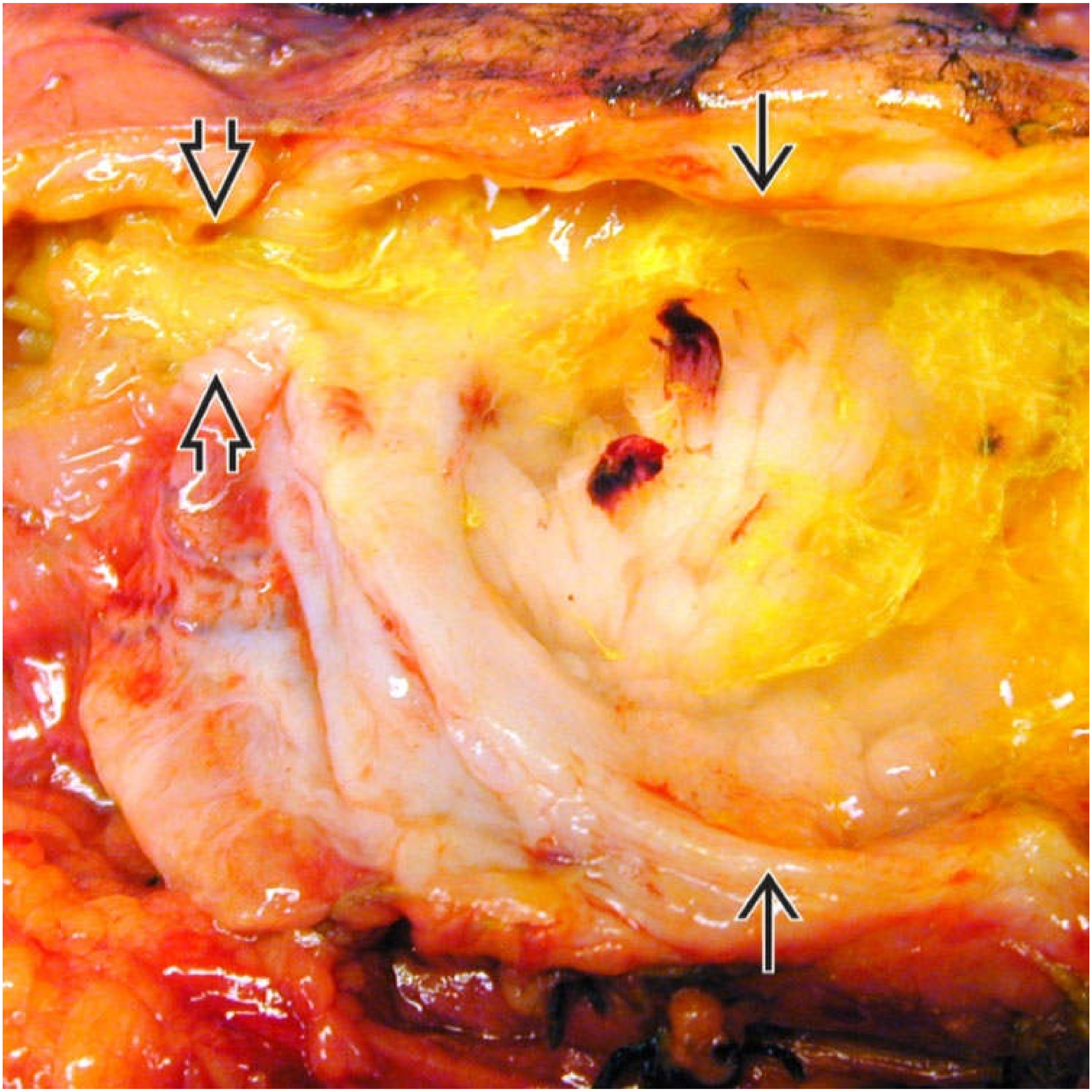
- Most common in pancreatic head
- Often involve only portion of pancreatic duct but may be multifocal or involve entire duct

Microscopic

- Composed of flat or papillary mucinous epithelium
  - 4 epithelial subtypes
  - Gastric

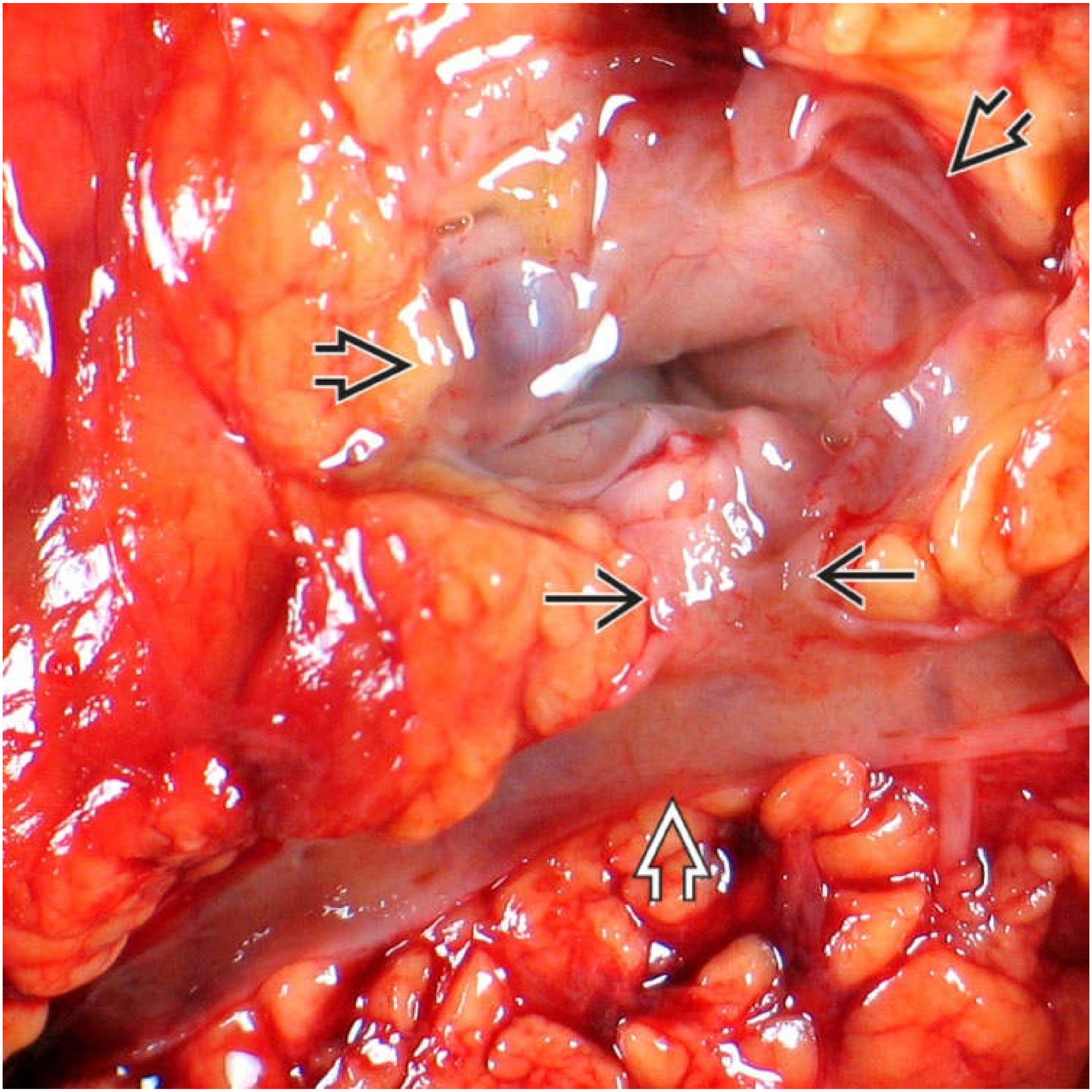
- Intestinal
- Pancreatobiliary
- Oncocytic

• 2-tiered dysplasia grading system (low- vs. high-grade dysplasia)

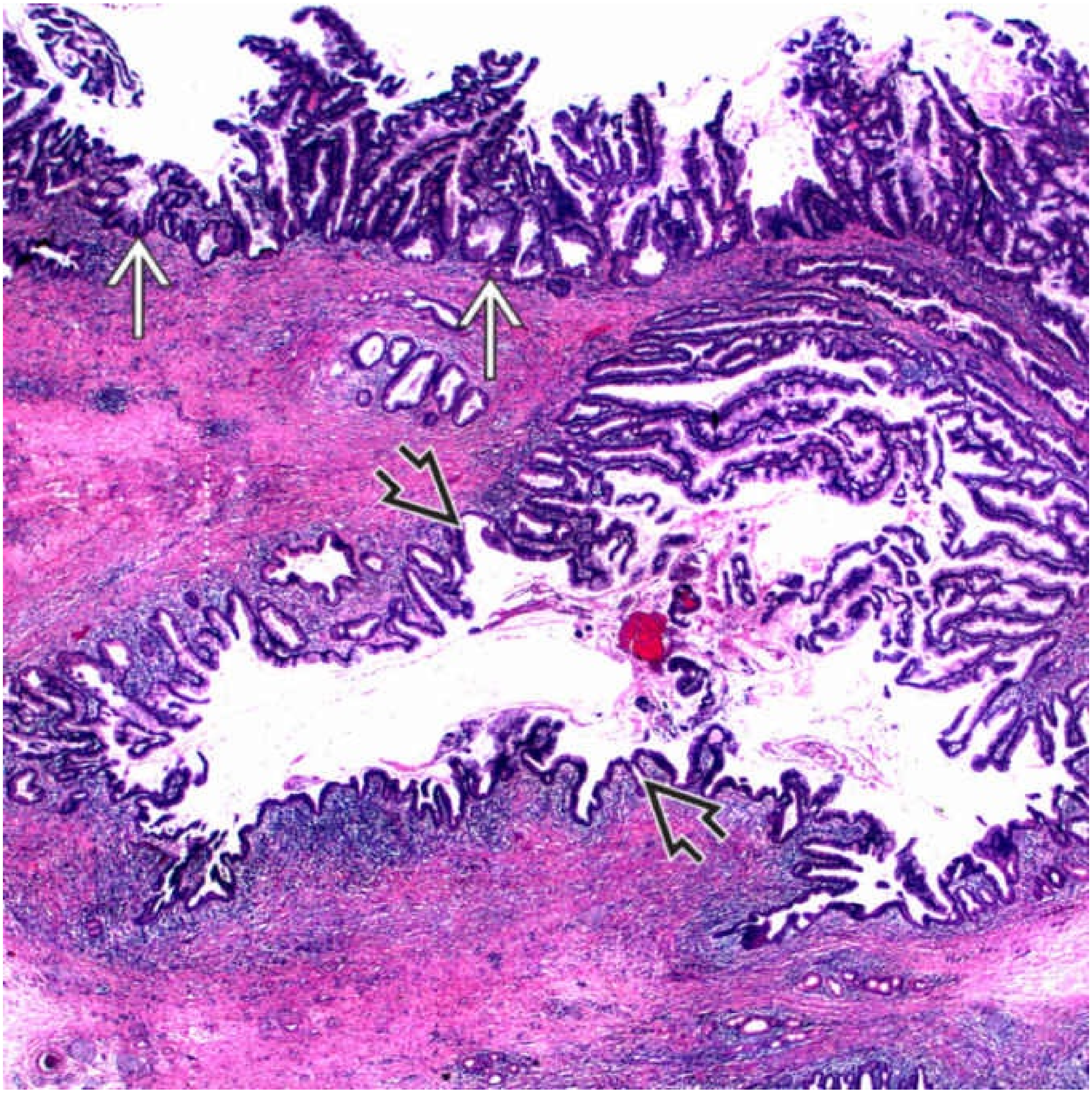


Main Duct IPMN

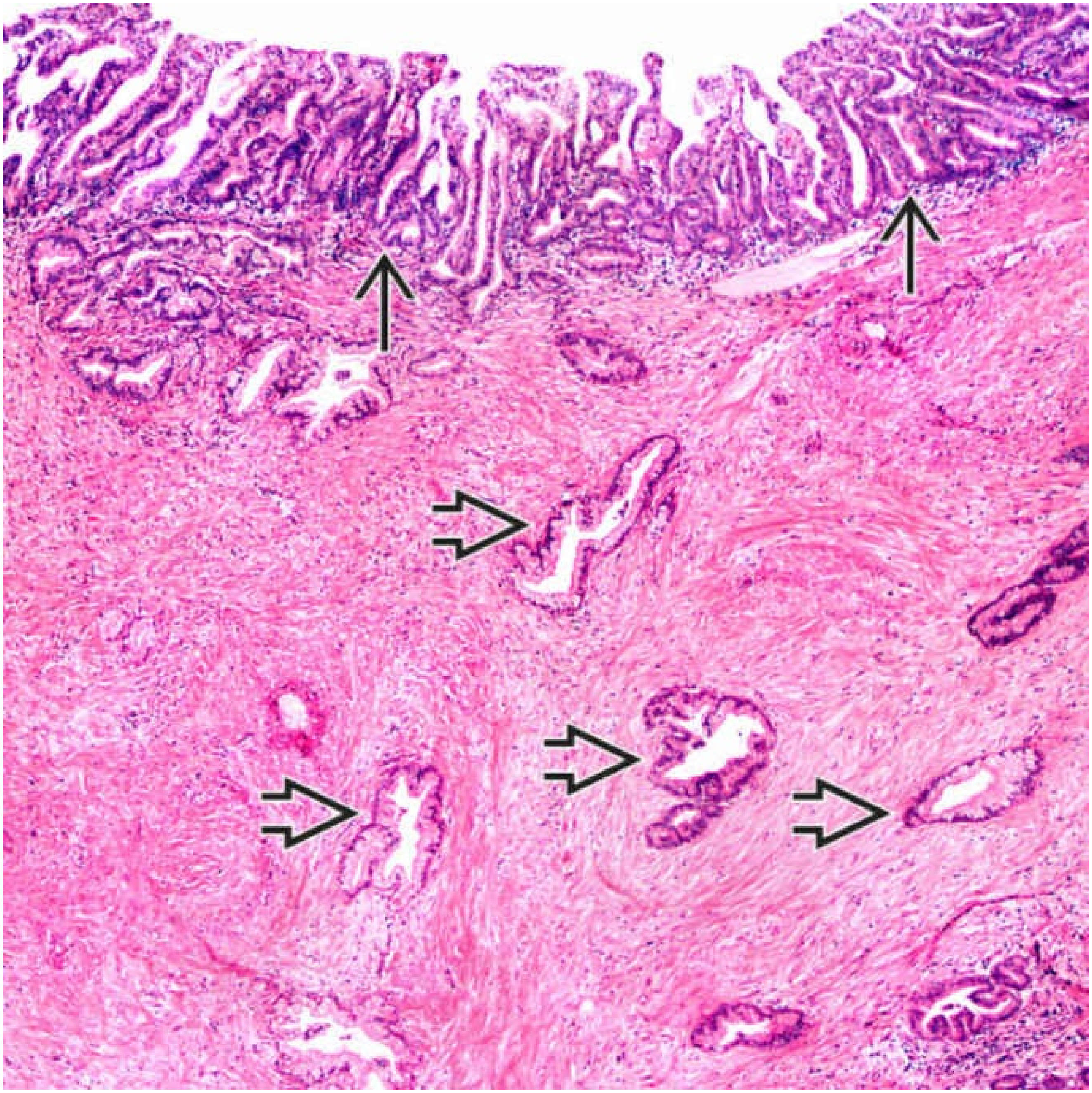
The markedly dilated main pancreatic duct → contains nodular mucosa and abundant mucin (stained with yellow dye). The ampullary orifice is indicated ⇨. A dilated patulous ampulla with extruded mucin is a typical appearance of this tumor on endoscopy.



Branch Duct IPMN
Gross photo shows a small cyst with a smooth lining ⇨ connected to the main pancreatic duct ⇨ via a dilated branch duct → .



Mixed Main Duct and Branch Duct Tumor
H&E shows an intraductal neoplastic papillary epithelial proliferation in both the main duct ⇒ and a large branch duct ➪. The stroma is dense and fibrotic.



Invasive Adenocarcinoma
Invasive tubular adenocarcinoma arising in association with intraductal papillary mucinous neoplasm (IPMN) is shown. The main duct contains intermediate- to high-grade dysplastic epithelium →. The infiltrating neoplastic glands ⇨ are of pancreatobiliary type.

TERMINOLOGY

Abbreviations

- Intraductal papillary mucinous neoplasm (IPMN)

Definitions

- Grossly visible, mucin-producing epithelial neoplasm present within main pancreatic duct &/or its branches
  - Subclassification based on duct(s) involved

- ○ Main duct type
  - – Mucinous epithelium confined to main pancreatic duct
- ○ Combined type
  - – Mucinous epithelium involving both main duct and branch ducts
- ○ Branch duct type
  - – Mucinous epithelium confined to branch ducts

ETIOLOGY/PATHOGENESIS

Molecular Features

- DPC4/SMAD4 loss uncommon, in contrast to high-grade PanIN and invasive ductal adenocarcinoma
- Overexpression of EGFR and ERBB2 common
- *KRAS* mutations common except for oncocytic type
- Loss of p16 increases with grade of dysplasia

Risk Factors

- History of diabetes
- Family history of pancreatic ductal adenocarcinoma (associated with branch duct IPMN)

CLINICAL ISSUES

Epidemiology

- Incidence
  - ○ 20-50% of resected cystic pancreatic tumors
    - – Incidence increasing due to increased incidental detection on imaging for other reasons
    - – Prevalence in general population estimated to be as high as 13.5% based on imaging studies
- Age
  - ○ Range: 25-94 years
    - – Average: Mid 60s
- Sex
  - ○ Slightly more common in men but varies according to ethnicity

Presentation

- Most patients asymptomatic
  - Symptomatic patients usually present with vague complaints related to duct obstruction/low-grade pancreatitis
  - ○ Abdominal &/or back pain
  - ○ Anorexia
  - ○ Weight loss
- Symptoms often present for months to years before diagnosis established

Endoscopic Findings

- Mucin extravasation from patulous ampulla of Vater in ∼ 25% of cases, essentially diagnostic of intestinal-type IPMN

Treatment

- Surgical resection is treatment of choice
  - 80-98% of IPMNs are surgically resectable

Prognosis

- Noninvasive tumors: 5-year survival rate: > 75%
  - Invasive tumors: 5-year survival rate is significantly lower (34-62%) than for noninvasive tumors
  - Still significantly better than that of conventional pancreatic ductal adenocarcinoma
- Increased incidence of synchronous or metachronous malignancies, particularly stomach and colon

IMAGING

CT Findings

- Main duct or combined type
  - Markedly dilated main duct often associated with dilated large branch ducts
- Branch duct type
  - Single or numerous cysts that represent dilated branch ducts

ERCP Findings

- Dilated main pancreatic duct &/or branch ducts in absence of stricture
- Filling defects due to papillary projections of neoplasm &/or mucus plugs

MRCP Findings

- In addition to dilated ducts, mural nodules better visualized
  - Indicative of higher grade lesion

MACROSCOPIC

General Features

- Most common in pancreatic head
  - Often involve only portion of pancreatic duct
  - Some are multifocal
  - Entire gland may be involved
- Main duct and combined types
  - Florid papillary projections, often in background of dilated ducts

- Branch duct type
  - Single or multiple peripheral cysts that connect to main duct, often with smooth lining
- Mural nodules &/or solid components may be seen in IPMNs with invasion

MICROSCOPIC

Histologic Features

- Flat or papillary mucinous epithelium
  - Dense fibrotic stroma (not ovarian type)
  - 4 epithelial subtypes
  - **Gastric (null) type**
    - – Histologically low grade
    - – Basally located nuclei
    - – Slightly eosinophilic cytoplasm
    - – Abundant apical cytoplasmic mucin
    - – Usually sole epithelial type in branch duct IPMNs, mixed with other epithelial types in main/combined types
  - **Intestinal type**
    - – Villous papillae with basophilic cytoplasm
    - – Enlarged, oval, hyperchromatic nuclei with pseudostratification
    - – Often have foci of high-grade dysplasia
  - **Pancreatobiliary type**
    - – Thin, branching papillae
    - – Amphophilic cytoplasm
    - – Enlarged, hyperchromatic nuclei
    - – Often associated with high-grade dysplasia
  - **Oncocytic type**
    - – Thick branching papillae with intracellular and intraepithelial lumina
    - – Abundant eosinophilic cytoplasm
    - – Large round nuclei with prominent nucleoli
    - – Some consider these to be separate type of neoplasm (intraductal oncocytic papillary neoplasm)
- 2-tiered dysplasia grading system
  - Low-grade dysplasia
    - – Uniform cells
    - – Only mild atypia
    - – No architectural complexity
    - – Lesions previously classified as moderate- or intermediate-grade dysplasia now included here
  - High-grade dysplasia/carcinoma in situ

- Marked architectural complexity
    - Marked nuclear atypia
    - Loss of nuclear polarity
    - Increased mitoses
  - Different grades of dysplasia often present within same IPMN
- 35% of main duct IPMN have associated invasive component; 15% of branch duct lesions
  - Invasive carcinomas arising in IPMN often have tubular features, reminiscent of pancreatic ductal adenocarcinoma, or colloid features
    - Intestinal-type IPMNs associated with colloid carcinoma
    - Pancreatobiliary-type IPMNs associated with tubular adenocarcinoma
    - Invasive carcinoma arising in association with gastric-type IPMN is rare; if present, has tubular features

Cytologic Features

- Small clusters and flat sheets of glandular epithelial cells
  - ± intracytoplasmic mucin

DIFFERENTIAL DIAGNOSIS

Mucinous Cystic Neoplasm

- Usually involves body/tail of pancreas
- Does not communicate with pancreatic ducts
- Younger women
- Presence of ovarian-like stroma required for diagnosis

Pancreatic Intraepithelial Neoplasm

- Does not produce grossly visible lesion
- Smaller than IPMN (usually < 5 mm in diameter)
- Overlap between these lesions can be difficult to resolve, especially at margins

Serous Cystic Neoplasm

- Often seen in women
- Microcysts lined by bland cuboidal epithelial cells with cytoplasmic glycogen
- Central scar seen in majority
- Does not communicate with pancreatic ducts

Retention Cyst

- Usually unilocular and lined by nonmucinous, pancreatic duct epithelium

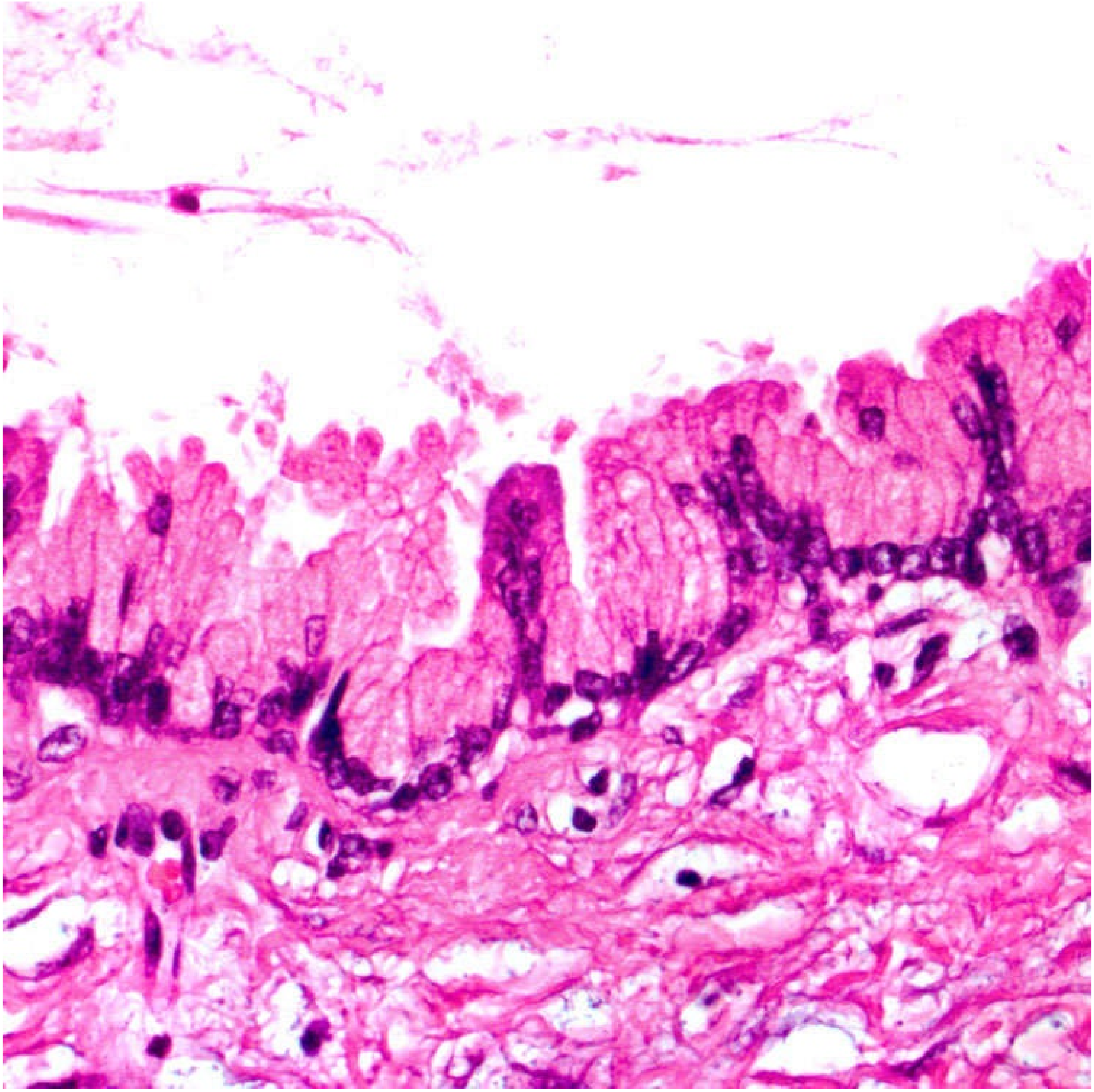
Solid Pseudopapillary Neoplasm

- Usually in younger women
- Contains areas of necrosis and hemorrhage
- Composed of poorly cohesive, uniform neoplastic cells that form pseudopapillae
- Does not communicate with pancreatic ducts

DIAGNOSTIC CHECKLIST

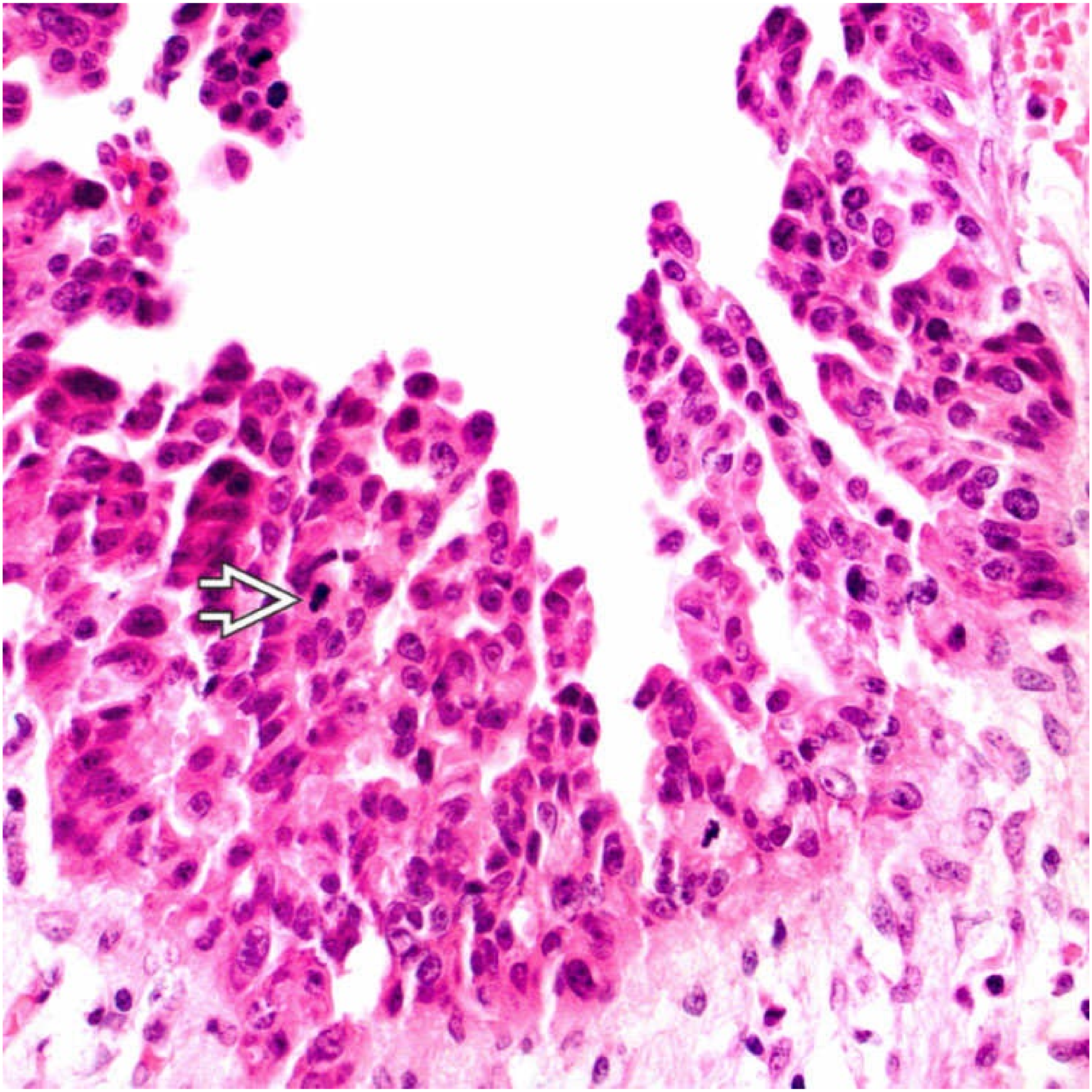
Clinically Relevant Pathologic Features

- Invasive components may be very focal, thus submission of entire lesion necessary
  - Careful gross examination to document communication between tumor and pancreatic ductal system essential
  - Surgical margin evaluation
    - Low-grade lesions at margin not clinically actionable

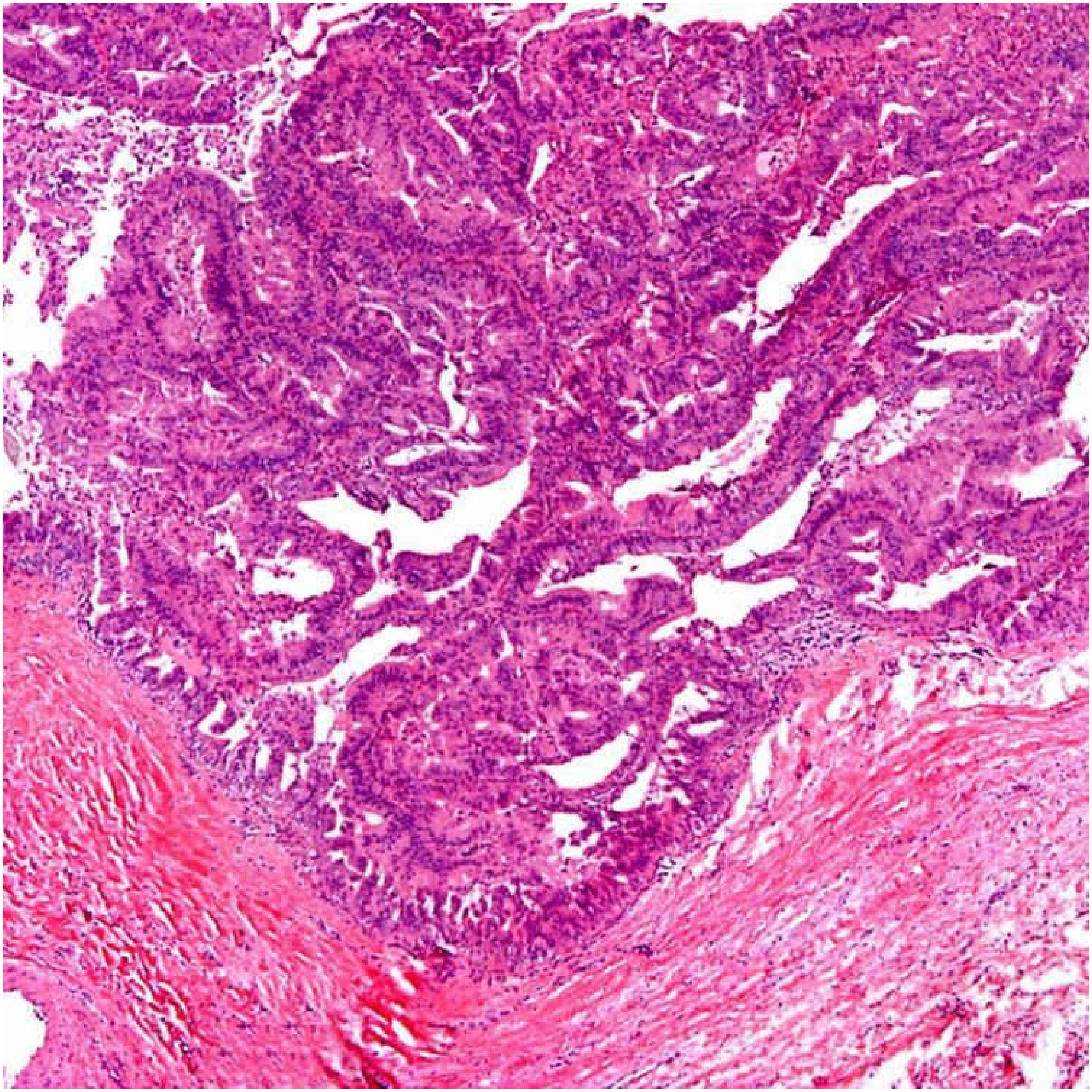


Low-Grade Dysplasia

Dysplasia in IPMN is graded with a 2-tiered system (low vs. high grade). The columnar cells with basally located small nuclei are typical of low-grade dysplasia. Lesions previously categorized as moderate or intermediate-grade dysplasia are now included in the low-grade category.

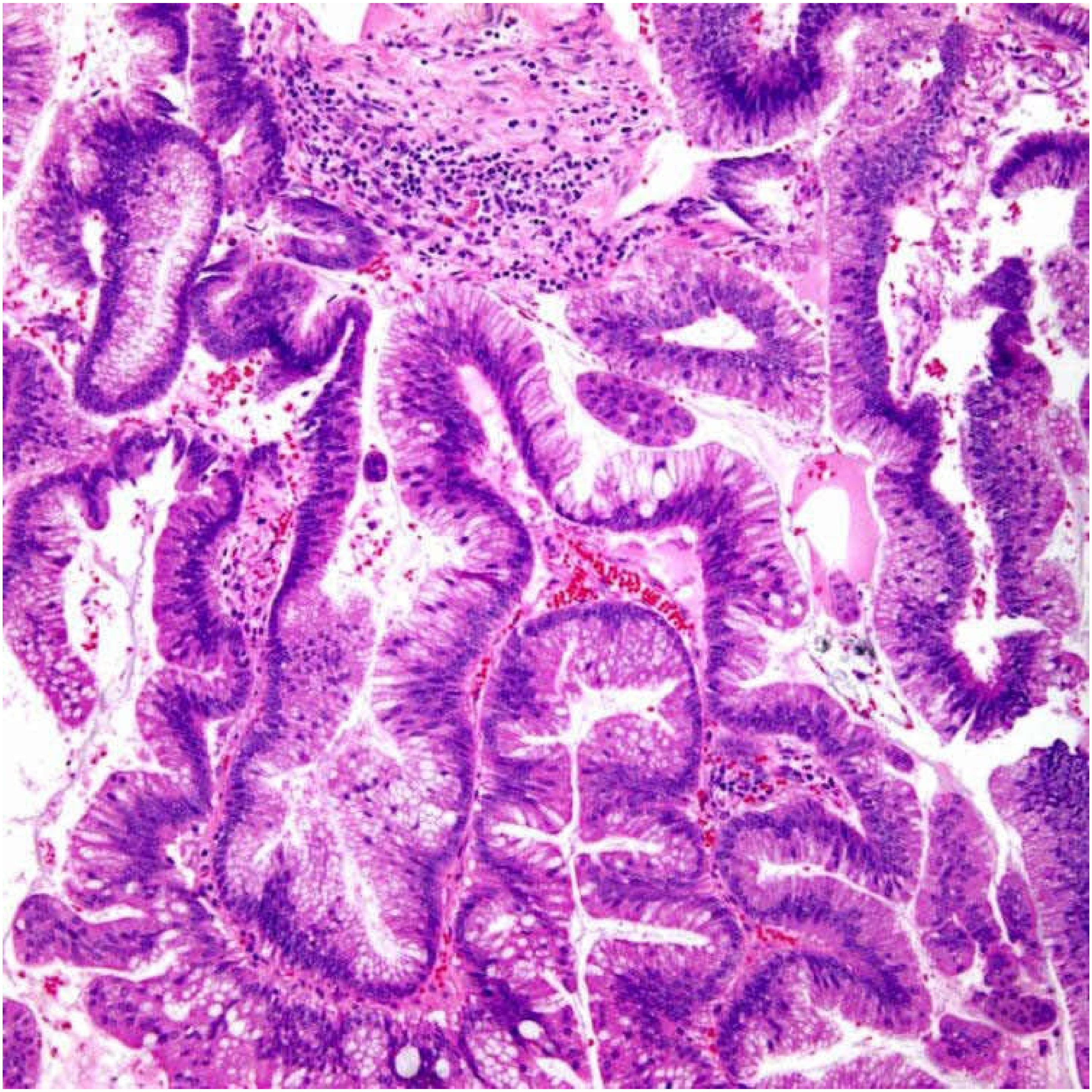


High-Grade Dysplasia
Micropapillary intraductal proliferation of tumor cells with a high N:C ratio indicates high-grade dysplasia. Scattered mitoses ⇨ are present.

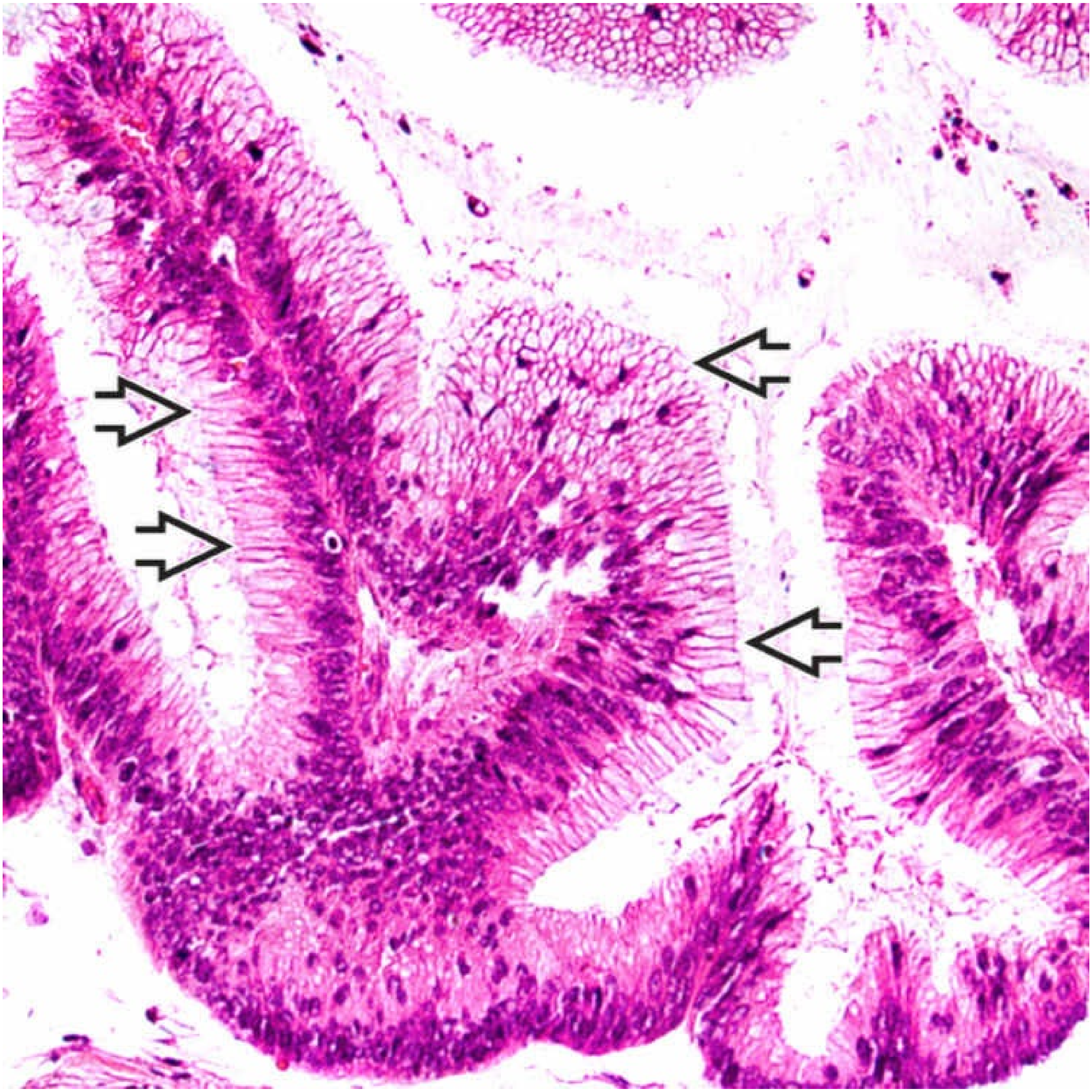


High-Grade Dysplasia

This main duct IPMN of pancreatobiliary type features a complex papillary proliferation with marked nuclear atypia, consistent with high-grade dysplasia. The term “high-grade dysplasia” should be reserved for carcinoma in situ type changes under the 2-tiered system.

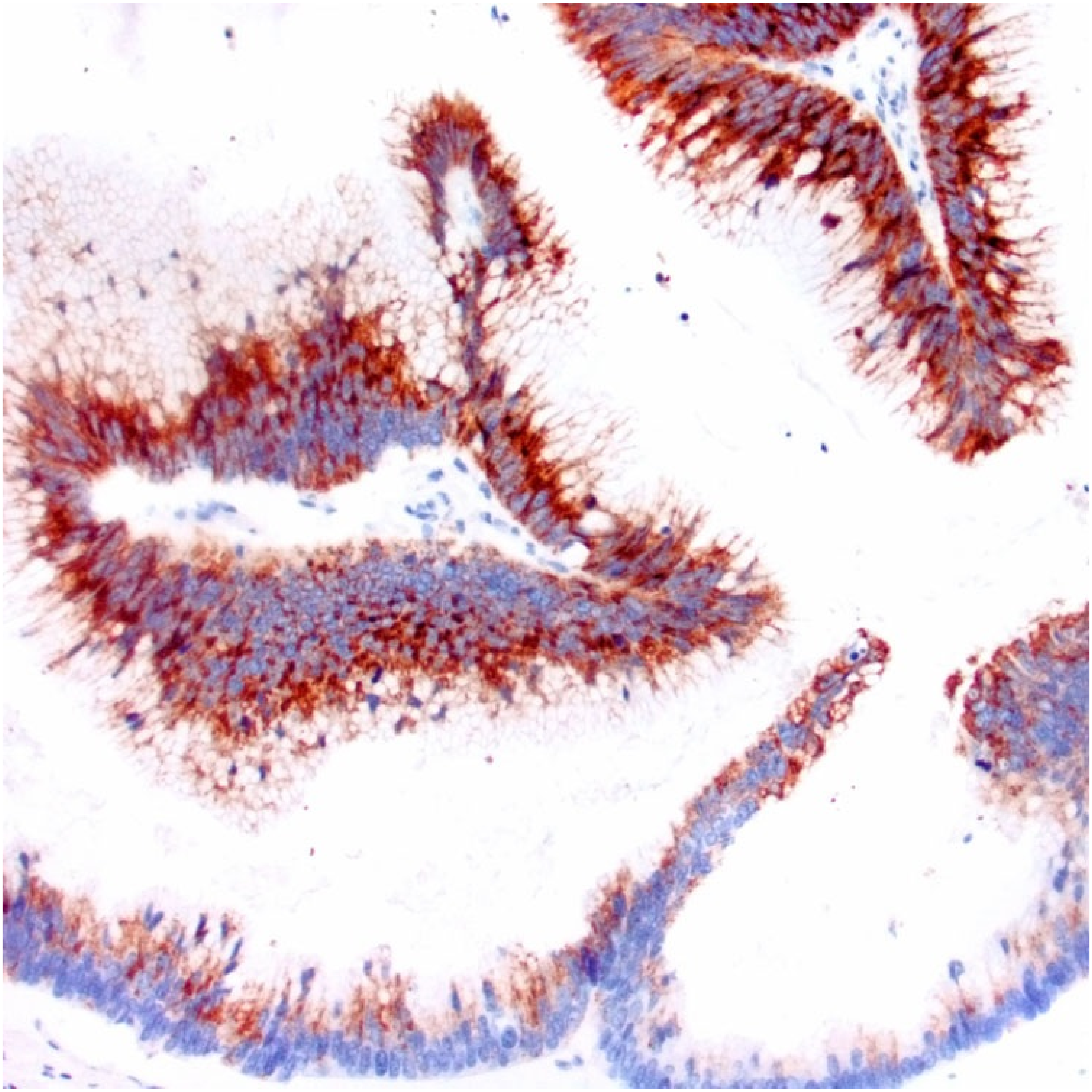


Intestinal Type
IPMN with intestinal-type epithelium shows nuclear pseudostratification and scattered goblet cells. This type is typically MUC6(-).

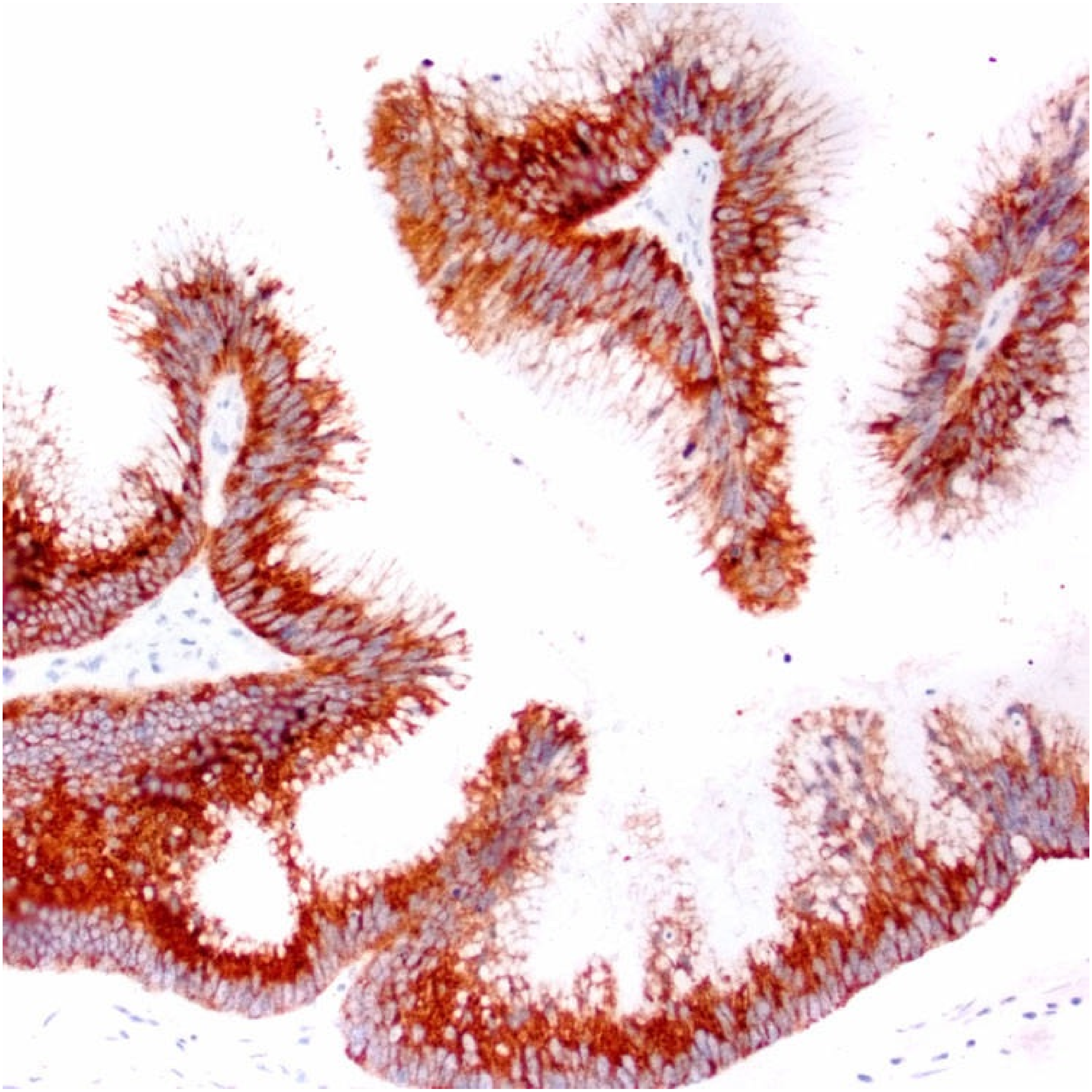


Intestinal Type

IPMN with intestinal-type epithelium is characterized by villous papillae with basophilic cytoplasm and elongated pseudostratified nuclei. Slightly amphophilic, apical mucin ⇨ is characteristic.

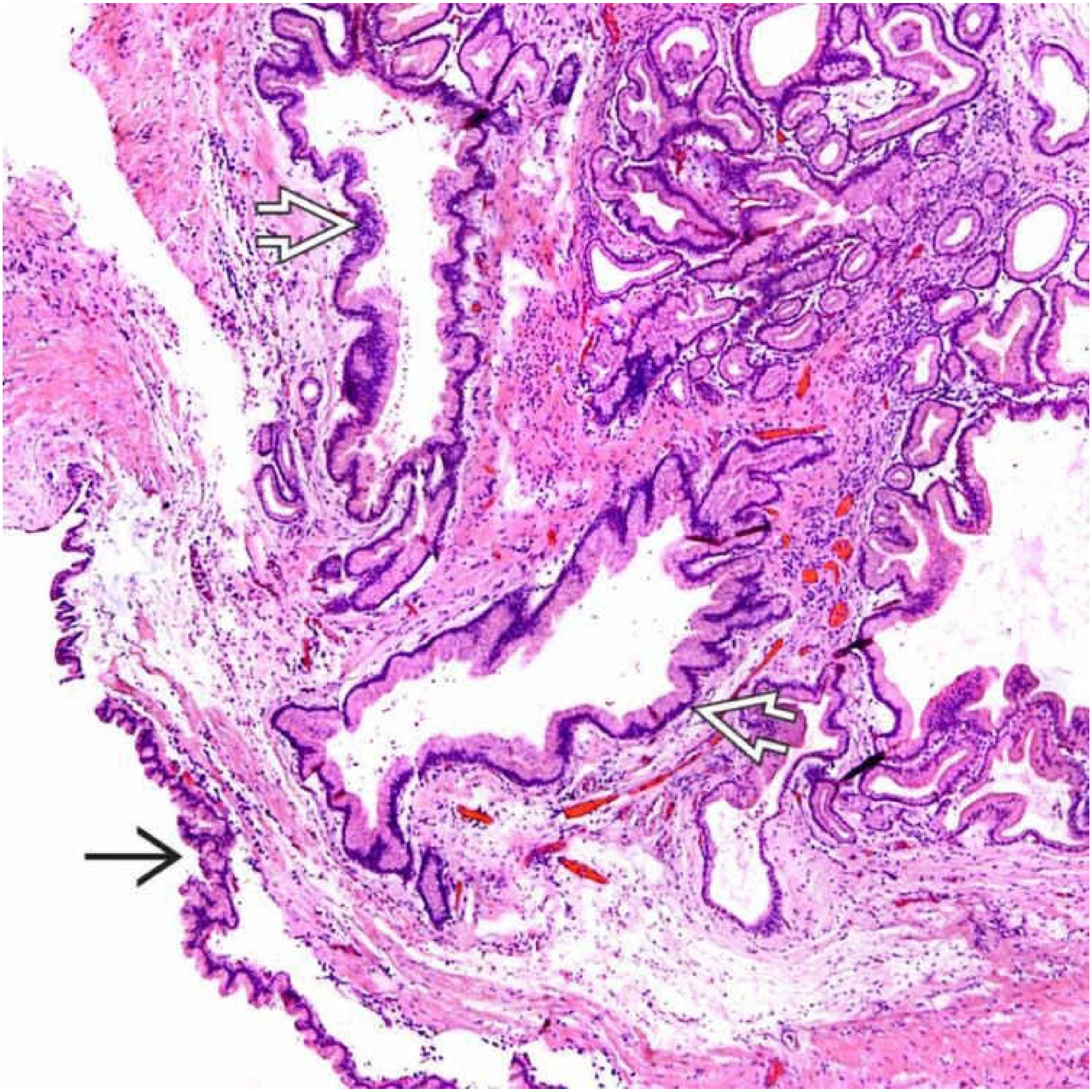


MUC5AC Stain
IPMN, intestinal type, demonstrates MUC5AC expression in the majority of neoplastic cells, a finding typical of intestinal-type cases even though this mucin is typically seen in gastric foveolar epithelium.

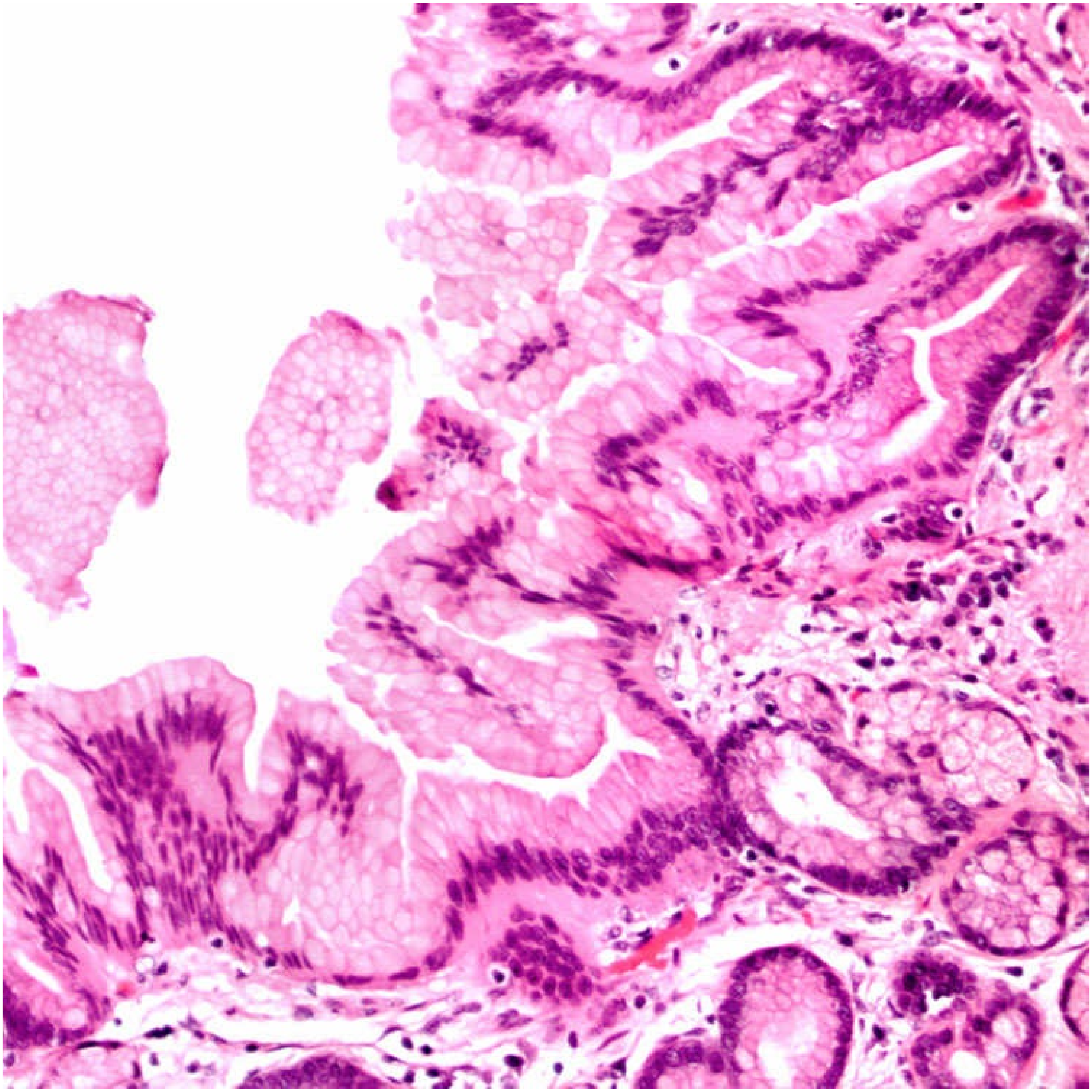


MUC2 Stain

IPMN, intestinal type, demonstrates diffuse MUC2 expression. This type is also characterized by nuclear expression of CDX-2. MUC1 expression (in an apical membranous pattern) is usually negative in intestinal type lesions but may be seen in high-grade tumors.

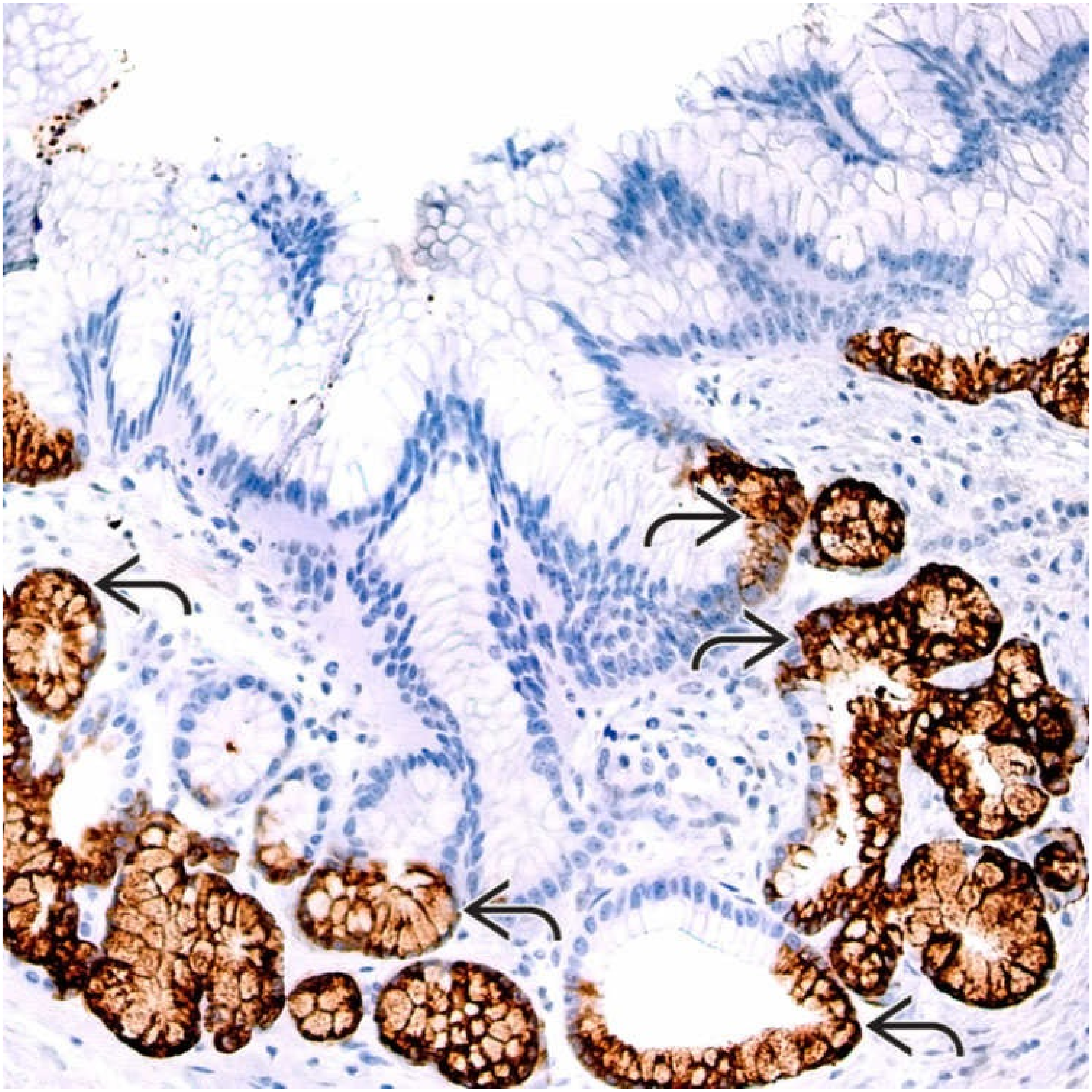


Gastric-Type IPMN, Low Grade
This IPMN contains gastric-type epithelium in the main → and branch ducts ⇨, and the degree of dysplasia is low grade throughout, which is typical of the gastric type.



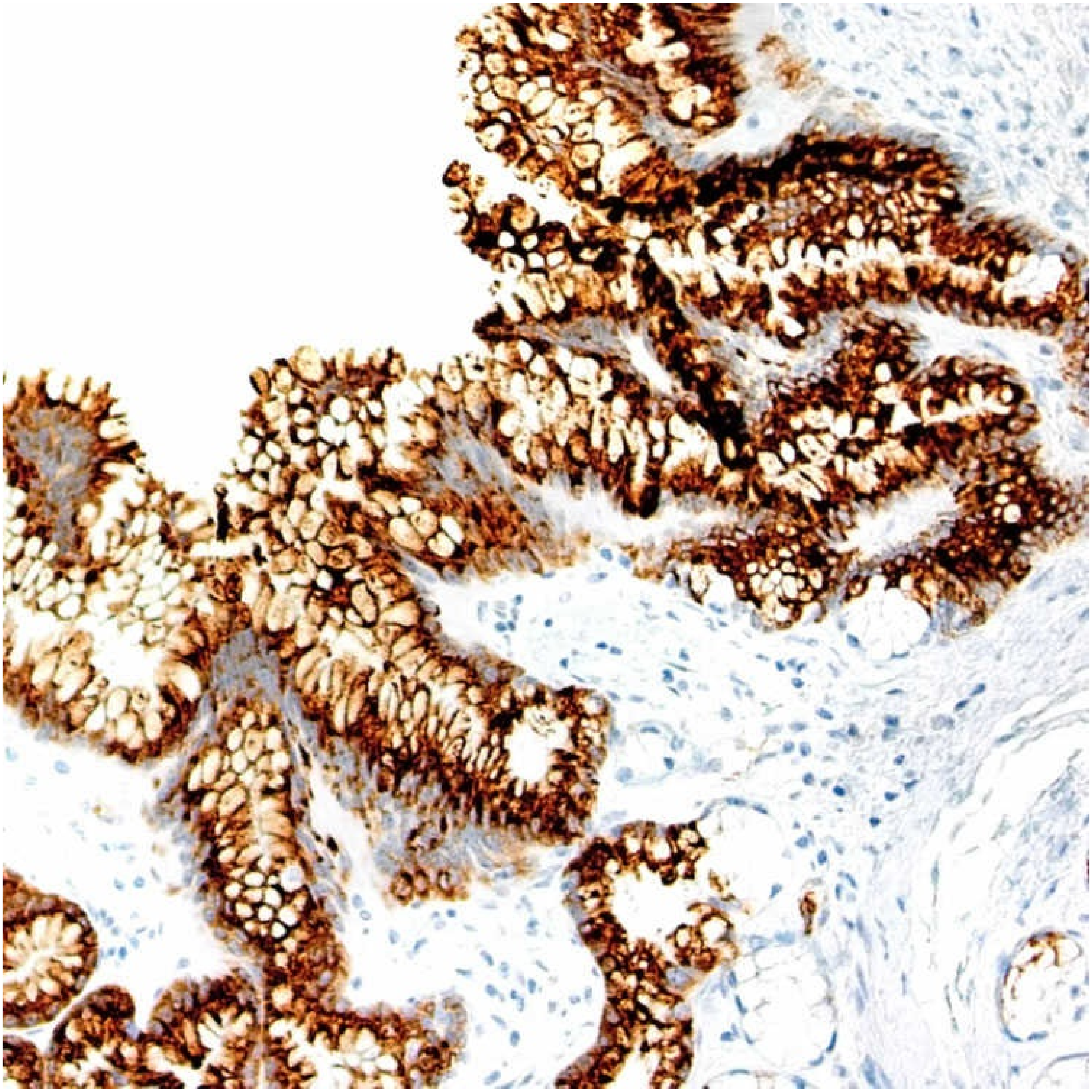
Gastric Type

IPMN, gastric type, is characterized by low-grade mucinous epithelium with abundant apical cytoplasmic mucin and small, basally located nuclei, reminiscent of gastric epithelium.

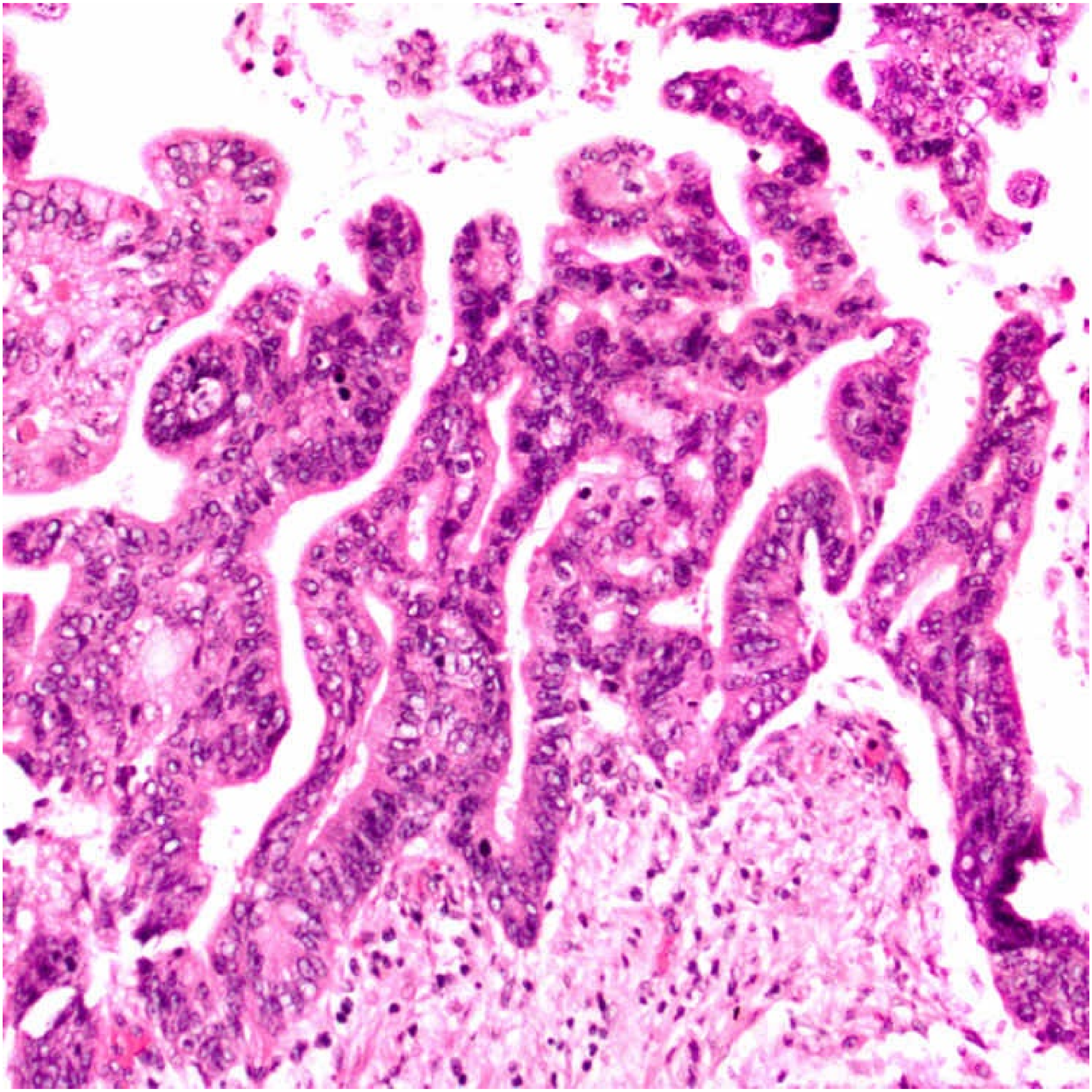


MUC6 Stain

IPMN, gastric type, demonstrates MUC6 expression in basal glands ↱ that resemble gastric pyloric glands. The combination of foveolar epithelium [MUC5AC(+)] and pyloric gland [MUC6(+)] type morphology and mucin phenotypes is reminiscent of gastric antrum.

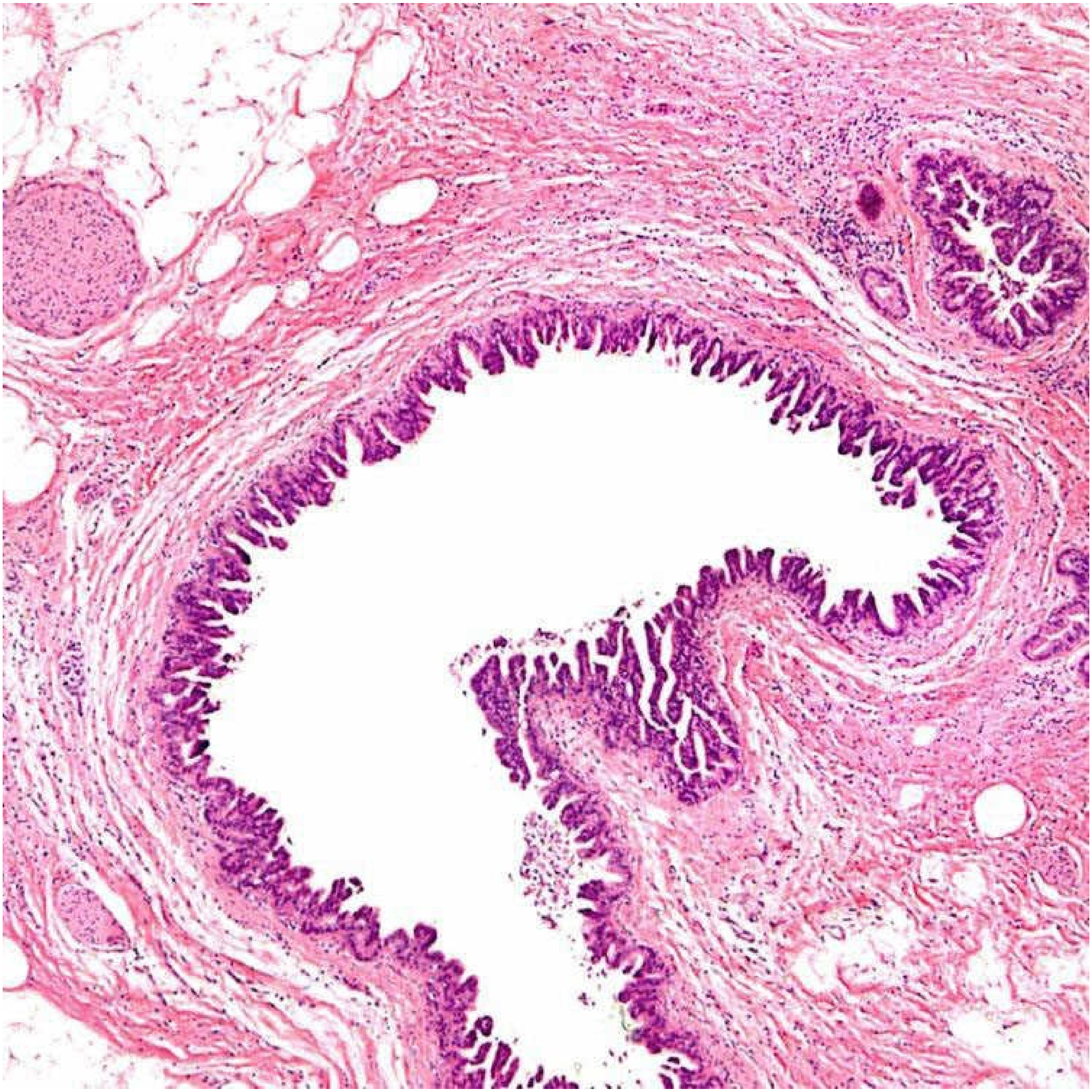


MUC5AC Stain
IPMN, gastric type, demonstrates diffuse MUC5AC expression. MUC5AC is typically found in gastric foveolar epithelium. MUC2, MUC1, and CDX-2 are also negative in gastric-type IPMN.

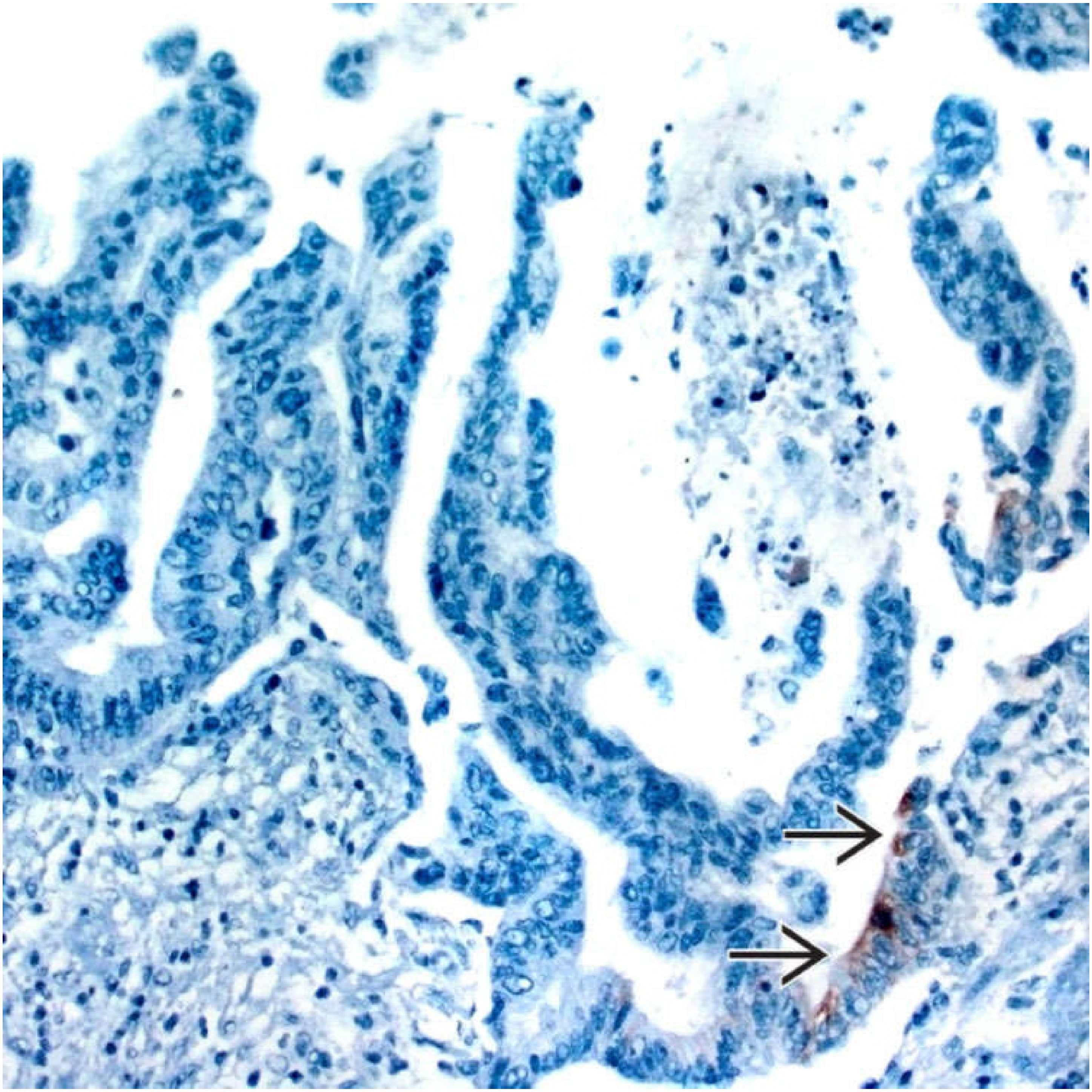


Pancreaticobiliary Type

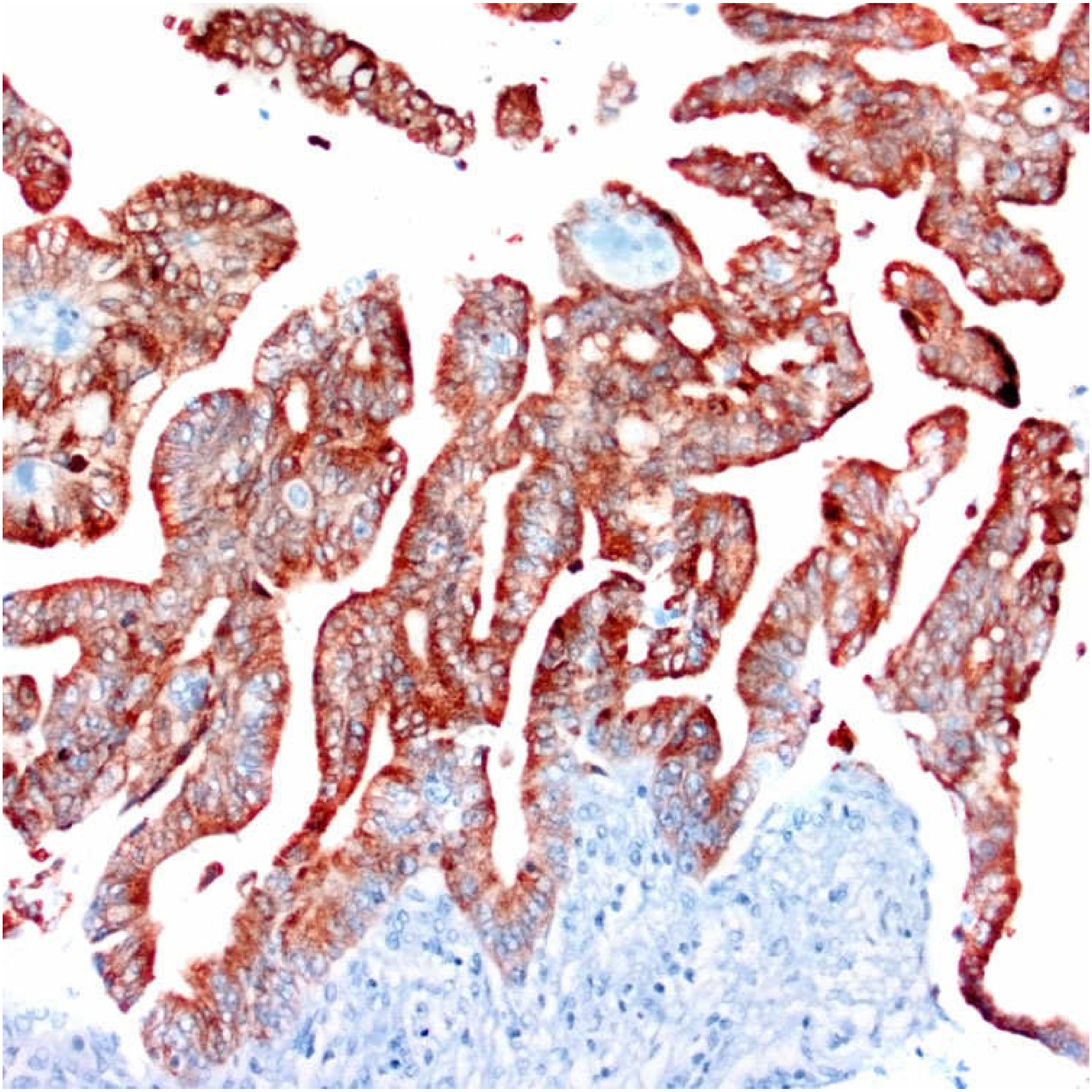
IPMN, pancreatobiliary type, is characterized by thin, branching complex papillae with moderate amphophilic cytoplasm and round, vesicular nuclei. This degree of nuclear atypia and architectural complexity indicates high-grade dysplasia.



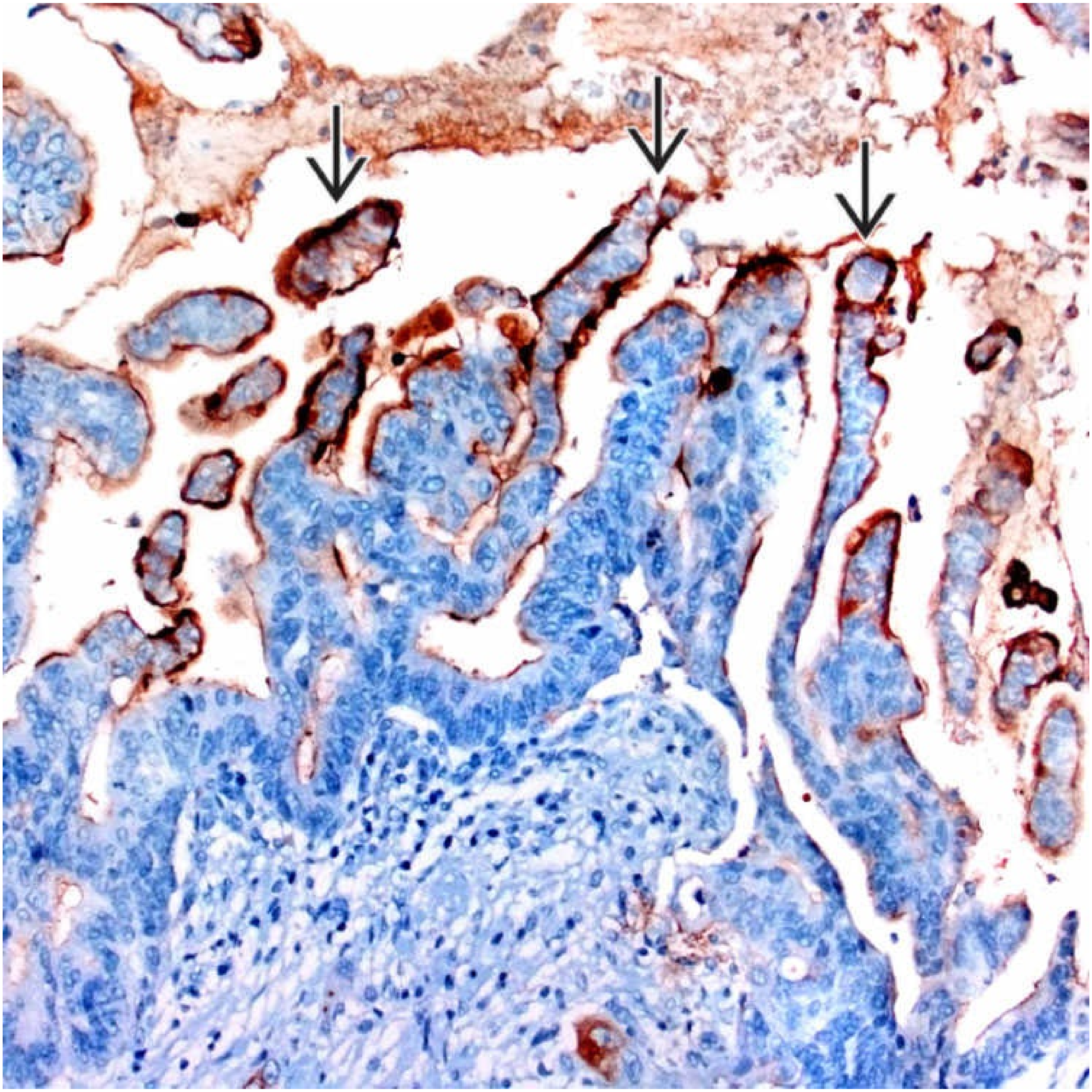
Pancreatobiliary Type
This pancreatobiliary-type IPMN involves the branch ducts. Note the dense fibrotic stroma.



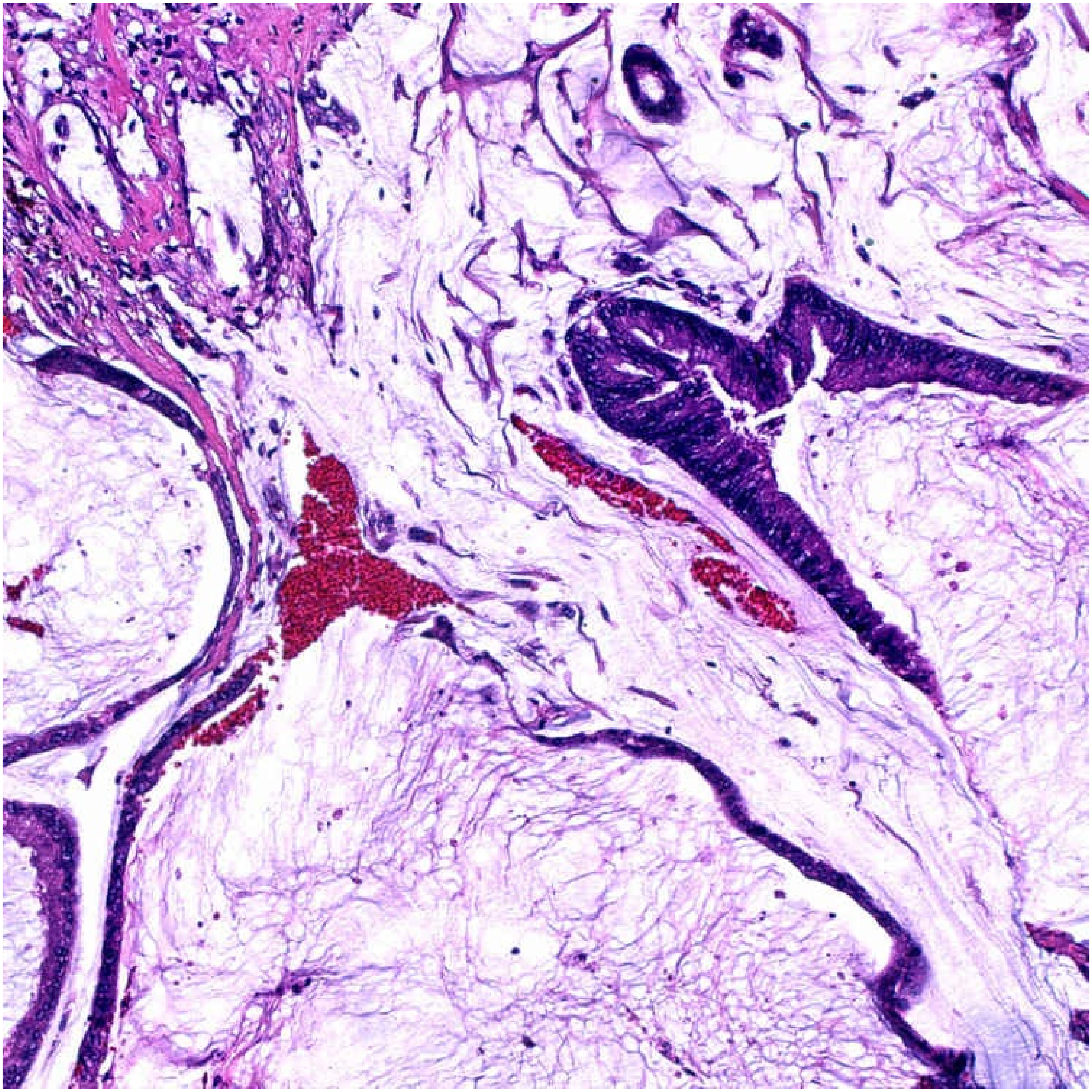
MUC6 Stain
IPMN, pancreatobiliary type, exhibits focal MUC6 expression →. MUC2 and CDX-2 are usually negative in pancreatobiliary-type IPMN.



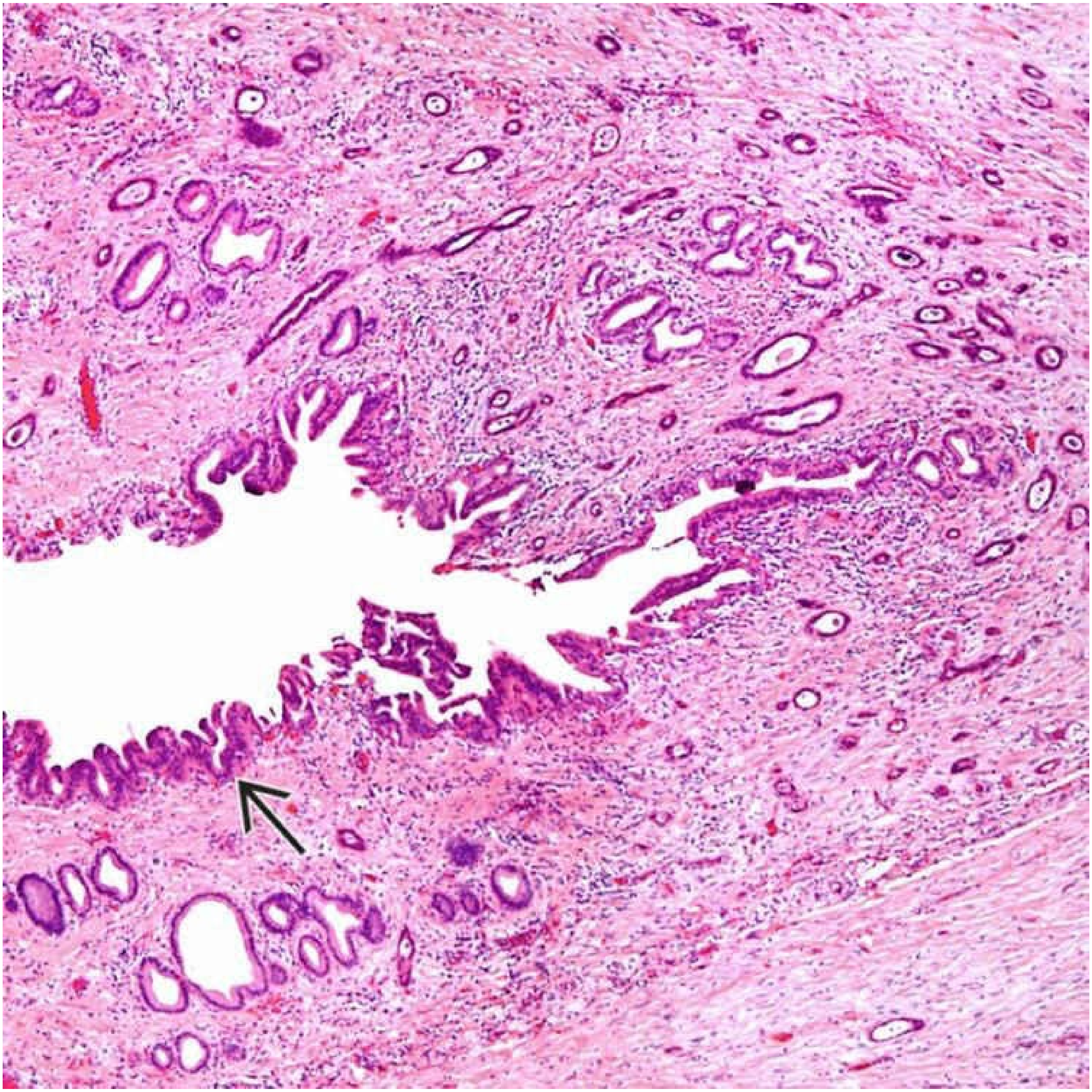
MUC5AC Stain
IPMN, pancreatobiliary type, shows diffuse MUC5AC expression.



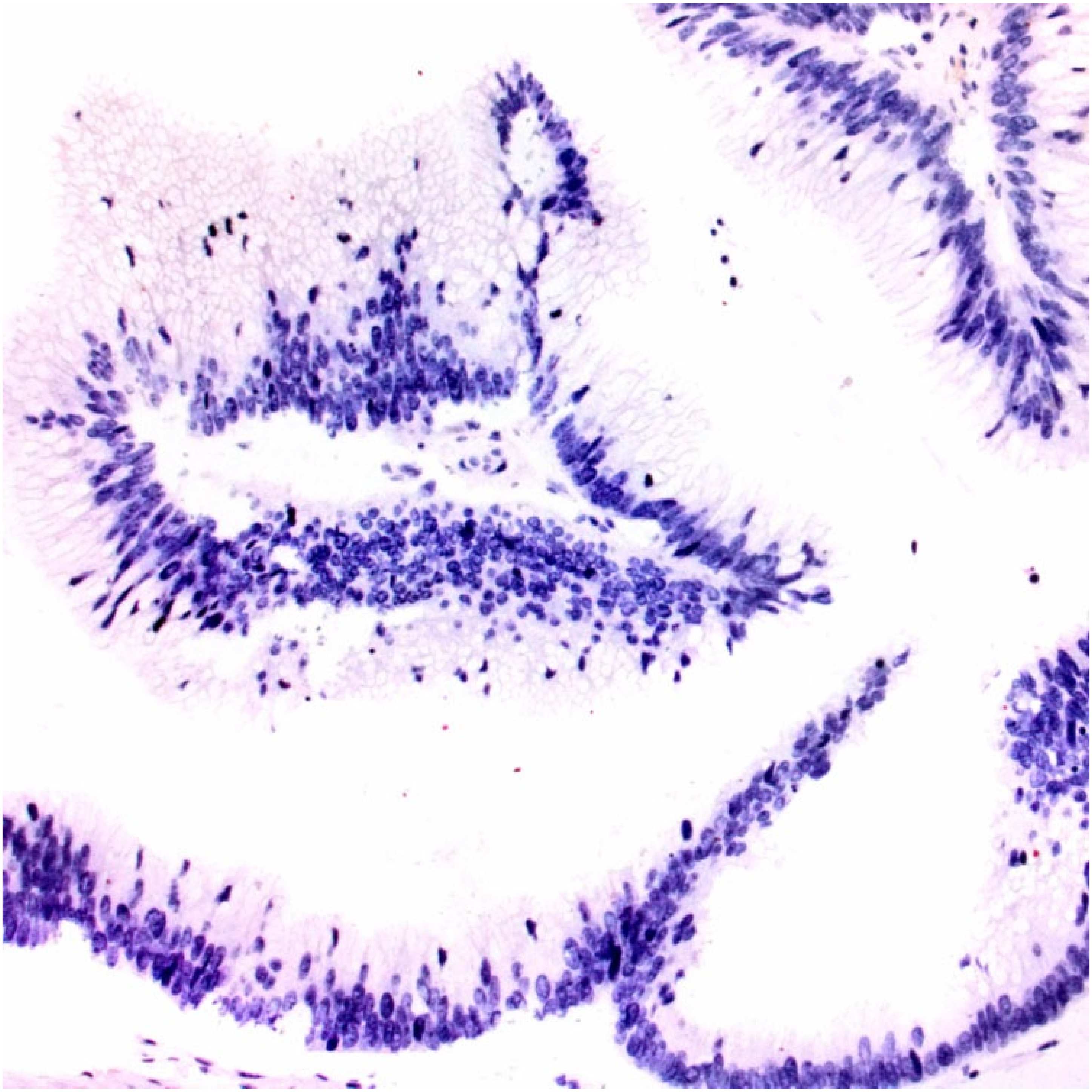
MUC1 Stain
IPMN, pancreatobiliary type, demonstrates MUC1 expression in an apical cytoplasmic membranous pattern →.



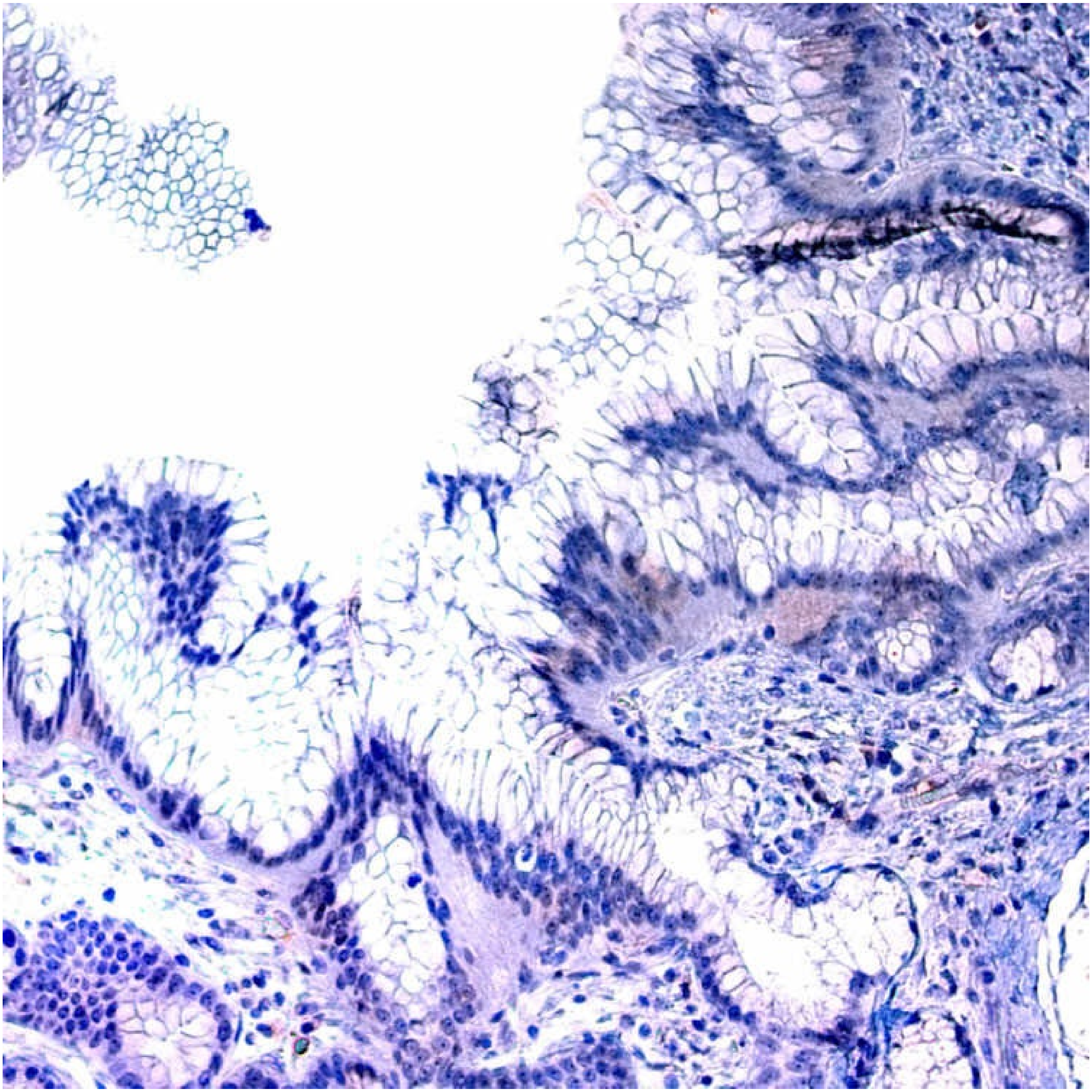
Colloid Carcinoma Arising in IPMN
This colloid carcinoma that arose in association with an intestinal-type IPMN features strips and nests of neoplastic epithelium present within mucin pools.



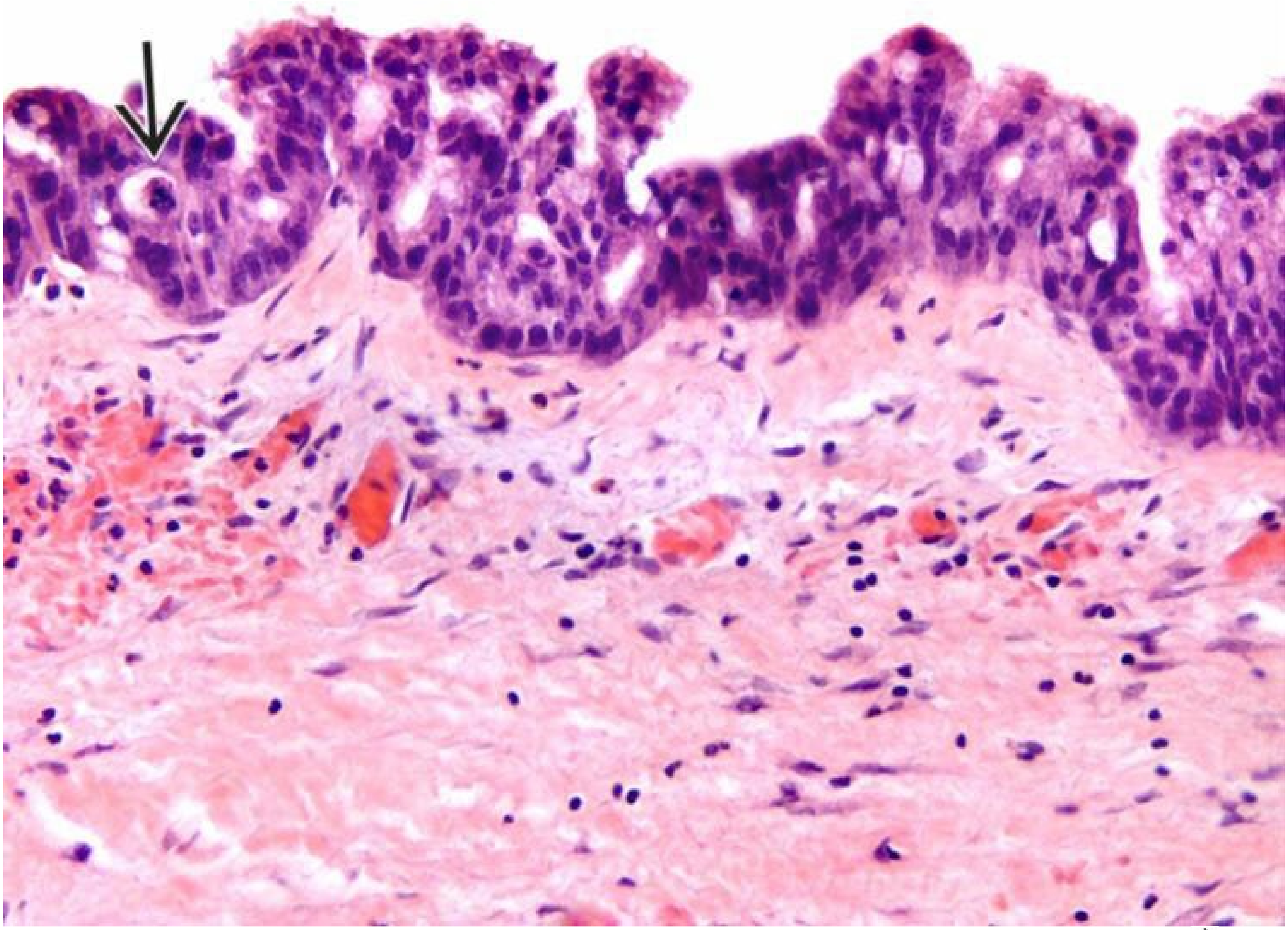
Tubular-Type Invasive Carcinoma
Tubular-type adenocarcinoma with well-formed neoplastic tubular glands arises from a duct → lined by IPMN with high-grade dysplasia.



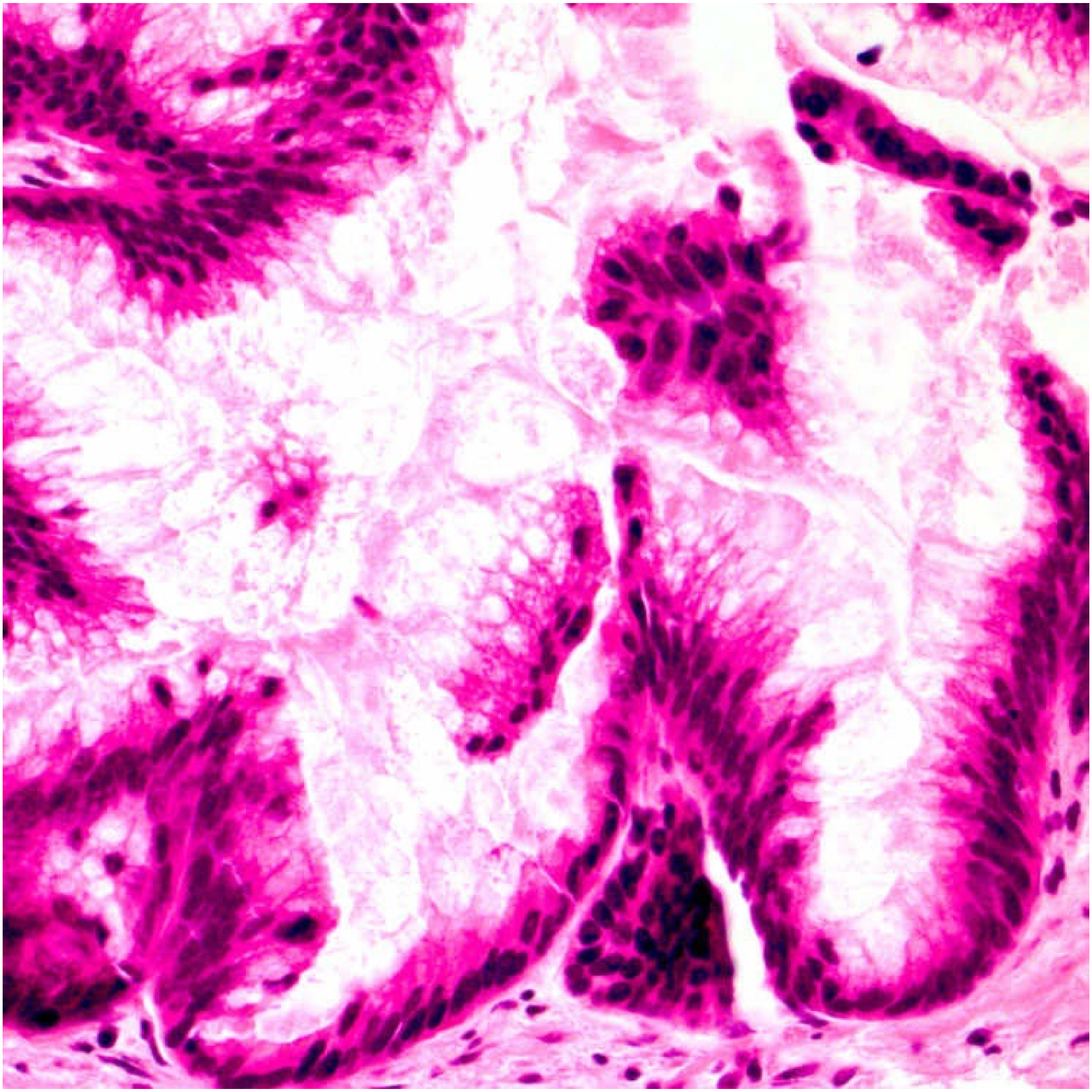
IPMN, intestinal type shows negative MUC6 expression. MUC1 expression (in an apical membranous pattern) may be seen in high-grade lesions but is usually negative in intestinal-type IPMN.



IPMN, gastric type demonstrates negative immunoreactivity to MUC2. CDX2 and MUC1 are also negative in gastric-type IPMN.



High-grade dysplasia featuring architectural complexity, nuclear atypia, and readily identifiable mitoses → is shown. The term “high-grade dysplasia” should be reserved for carcinoma-in-situ-type changes under the 2-tiered system.


H&E shows mucinous columnar cells with stratified, elongated nuclei.

SELECTED REFERENCES

1. Adsay, V, et al. Pathologic evaluation and reporting of intraductal papillary mucinous neoplasms of the pancreas and other tumoral intraepithelial neoplasms of pancreatobiliary tract: recommendations of Verona Consensus Meeting. *Ann Surg*. 2016; 263(1):162–177.
2. Basturk, O, et al. A Revised Classification System and Recommendations From the Baltimore Consensus Meeting for Neoplastic Precursor Lesions in the Pancreas. *Am J Surg Pathol*. 2015; 39(12):1730–1741.
3. Fritz, S, et al. Pancreatic intraductal papillary mucinous neoplasm – where is the challenge? *Dig Dis*. 2015; 33(1):99–105.

4. Klöppel, G, et al. Intraductal neoplasms of the pancreas. *Semin Diagn Pathol*. 2014; 31(6):452–466.
5. Basturk, O, et al. Preferential expression of MUC6 in oncocytic and pancreatobiliary types of intraductal papillary neoplasms highlights a pyloropancreatic pathway, distinct from the intestinal pathway, in pancreatic carcinogenesis. *Am J Surg Pathol*. 2010; 34(3):364–370.
6. Sahani, DV, et al. Multidisciplinary approach to diagnosis and management of intraductal papillary mucinous neoplasms of the pancreas. *Clin Gastroenterol Hepatol*. 2009; 7(3):259–269.
7. Ishida, M, et al. Characteristic clinicopathological features of the types of intraductal papillary-mucinous neoplasms of the pancreas. *Pancreas*. 2007; 35(4):348–352.
8. Tanaka, M, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. *Pancreatology*. 2006; 6(1-2):17–32.
9. Furukawa, T, et al. Classification of types of intraductal papillary-mucinous neoplasm of the pancreas: a consensus study. *Virchows Arch*. 2005; 447(5):794–799.
10. Adsay, NV, et al. Pathologically and biologically distinct types of epithelium in intraductal papillary mucinous neoplasms: delineation of an “intestinal” pathway of carcinogenesis in the pancreas. *Am J Surg Pathol*. 2004; 28(7):839–848.
11. Hruban, RH, et al. An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. *Am J Surg Pathol*. 2004; 28(8):977–987.

Intraductal Oncocytic Papillary Neoplasm

KEY FACTS

Terminology

• Grossly cystic neoplasm with intraductal growth pattern and oncocytic epithelium

Clinical Issues

• Rare entity with ~ 40 cases reported in literature
• Range: 20-80 years (average: 60s)
• M = F
• Majority present with nonspecific symptoms or discovered incidentally
• Surgical resection is treatment of choice
• 5-year survival rate of noninvasive IOPN: Approaches 100%
• 5-year survival rate of invasive IOPN: > 70%

Imaging

• Large masses within cystic lesion connected to dilated main pancreatic duct

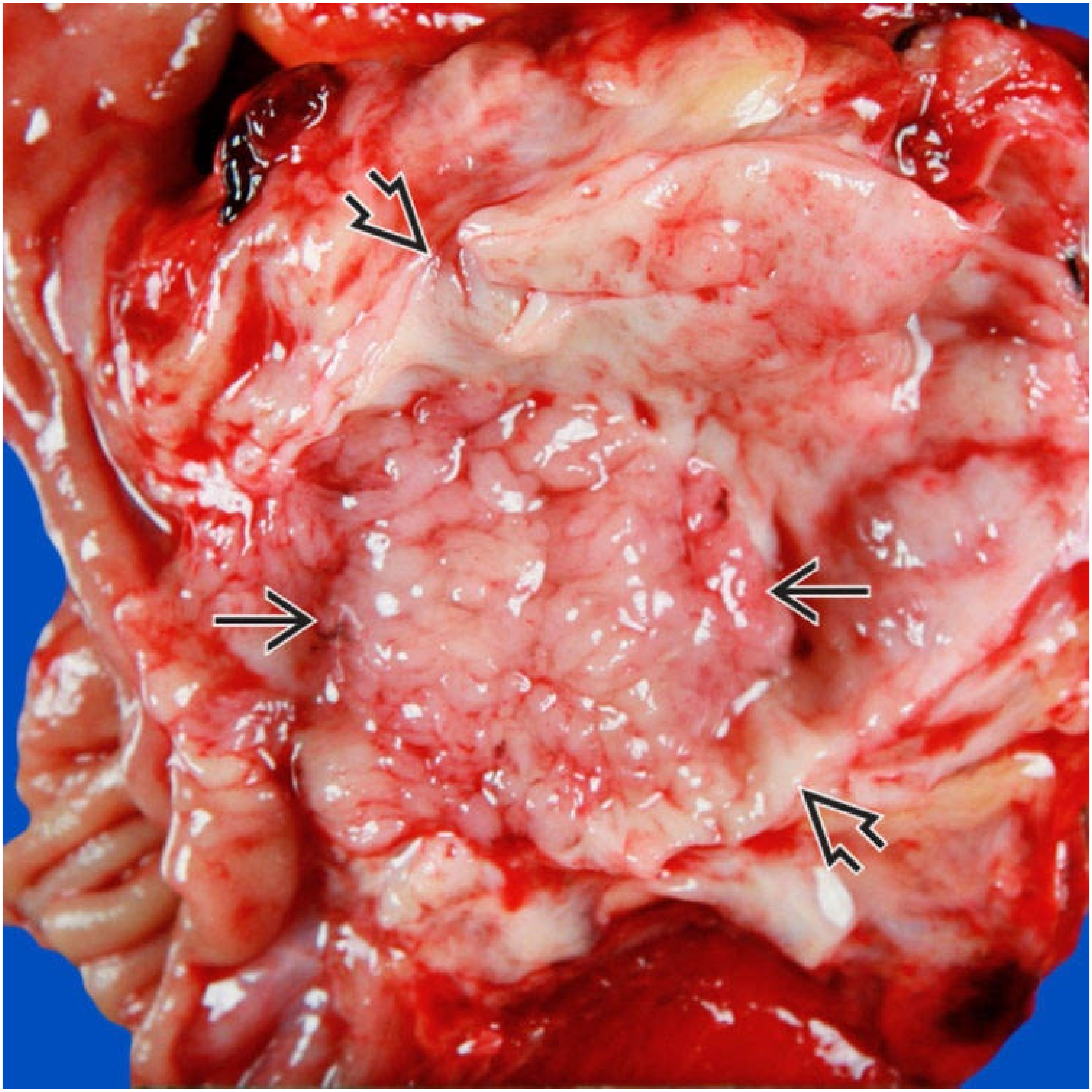
Macroscopic

• Usually unilocular or multilocular and cystic with soft red-brown or tan-red papillary masses
• Size range: 1.6-15 cm (average: 4-6 cm)

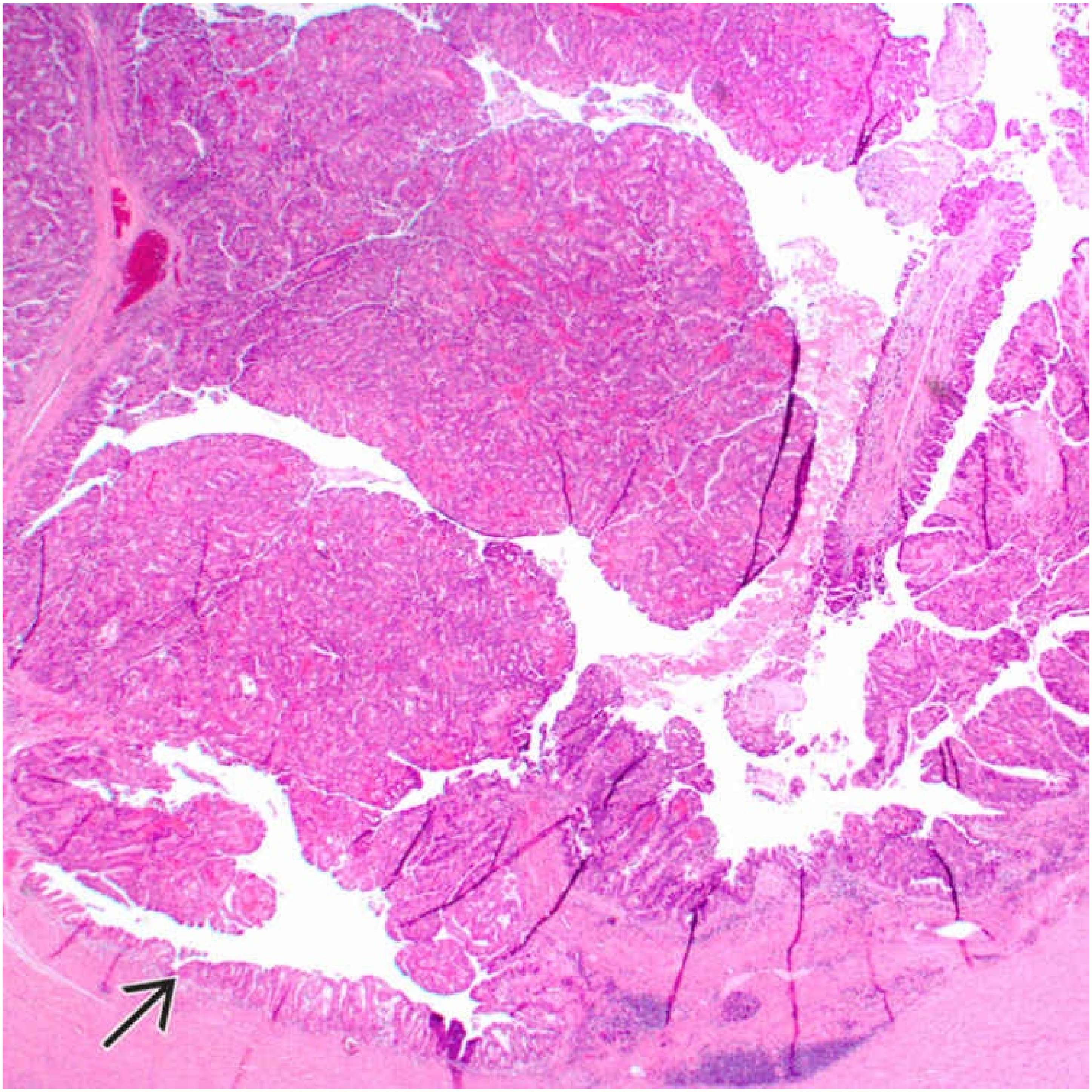
Microscopic

• Oncocytic epithelium that forms architecturally complex papillary growth pattern as well as areas of cribriforming and solid growth
  ○ Often classified as having high-grade dysplasia given architectural complexity
• Neoplastic cells have abundant granular eosinophilic cytoplasm with large nuclei, prominent nucleoli
• Both intracytoplasmic and intercellular lumina found, many containing mucin, with scattered goblet cells
• Stroma can be edematous or myxoid at tip &/or base of papillae

• Invasive carcinoma, often minimally invasive, present in 25-50%
• Stain strongly with MUC6
• Variable staining with MUC1, MUC2, MUC5AC, CEA, CA19-9

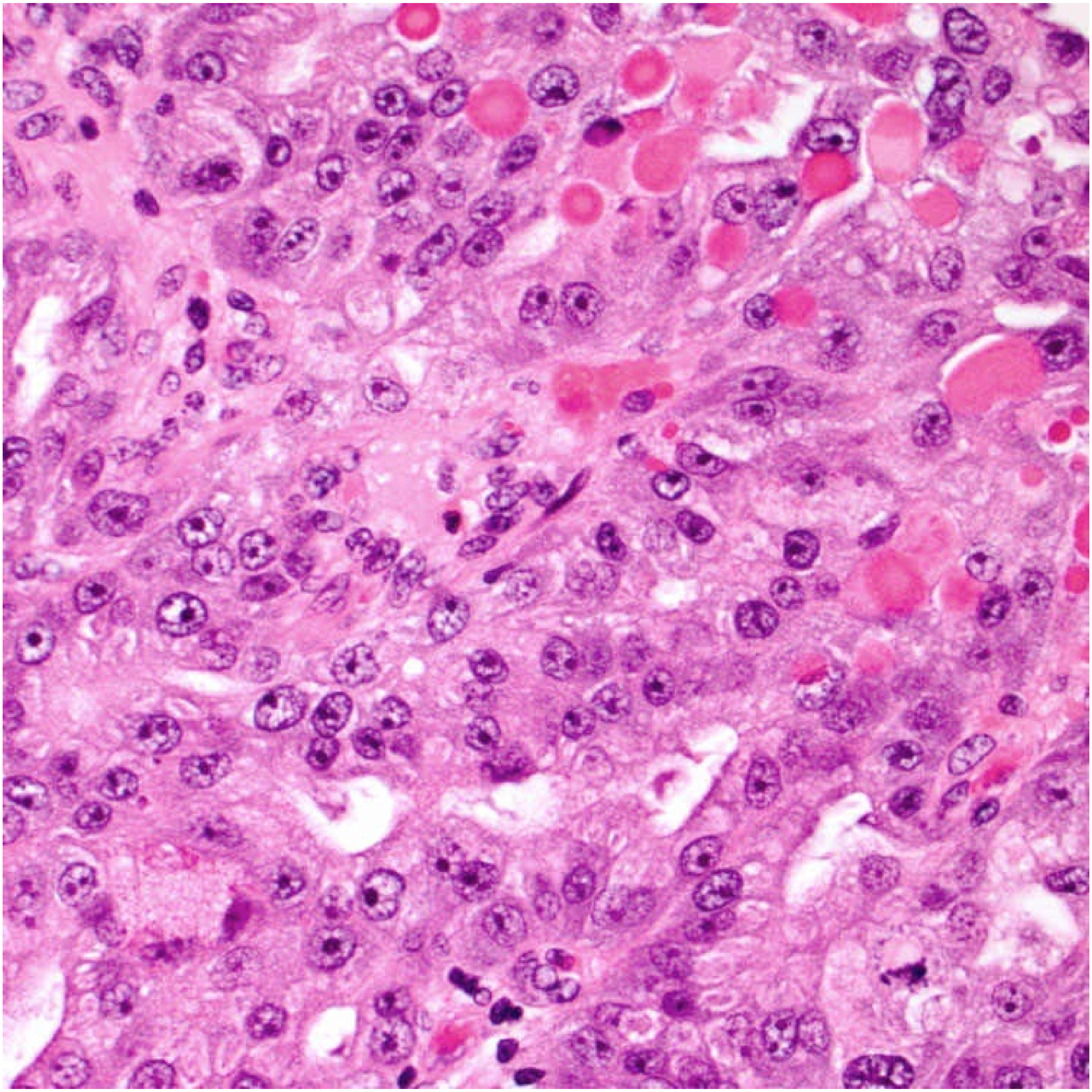


Gross Appearance
A tan-red luminal papillary mass → partially involves the dilated main pancreatic duct ⇨ .



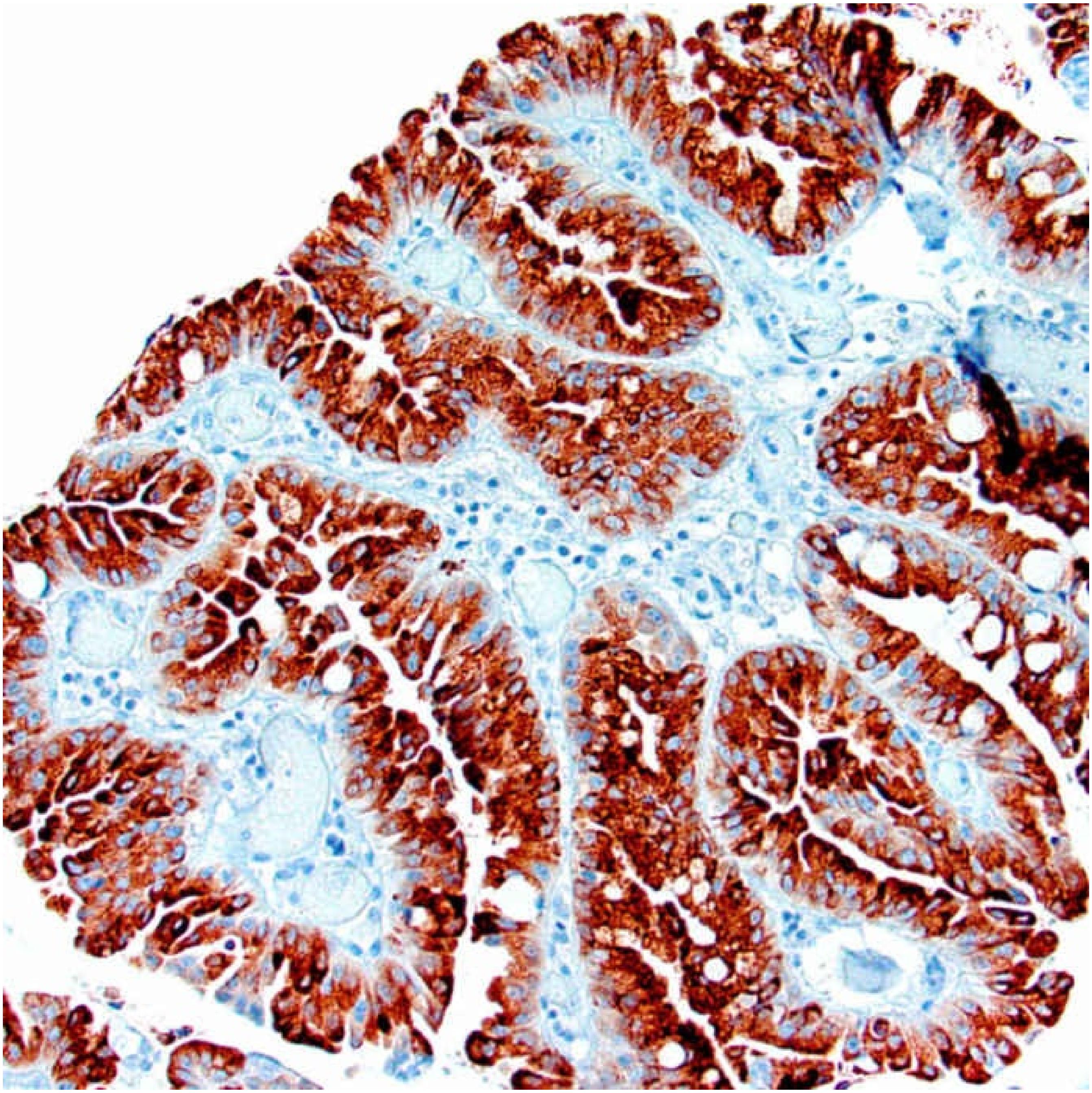
Dilated Branch Duct

Intraductal oncocytic papillary neoplasms (IOPNs) consist of architecturally complex, thick papillae, seen here growing in a dilated branch duct that is, in part, lined by relatively flat epithelium →.



Higher Magnification

Higher magnification of IOPN exhibits architecturally complex growth with cribriforming &/or solid nests. The neoplastic epithelial cells have abundant granular eosinophilic cytoplasm and large nuclei with prominent nucleoli.



MUC6 Expression
IOPNs demonstrate strong MUC6 expression.

TERMINOLOGY

Abbreviations

- Intraductal oncocytic papillary neoplasm (IOPN)

Definitions

- Grossly cystic neoplasm consisting of architecturally complex papillary **intraductal** growth of oncocytic (oxyntic) epithelium
- Grouped with intraductal papillary mucinous neoplasm (IPMN) in most recent WHO classification but considered distinct entity by others

CLINICAL ISSUES

Epidemiology

- Incidence
  - Rare entity with ~ 40 cases reported in literature
- Age
  - Range: 20-80 years (average: 60s)
- Sex
  - M = F

Presentation

- Similar to IPMNs
- Majority present with nonspecific symptoms or are discovered incidentally during imaging study for another indication

Treatment

- Surgical resection is treatment of choice

Prognosis

- 5-year survival rate of noninvasive IOPN: Approaches 100%
- 5-year survival rate of invasive IOPN: > 70%

IMAGING

General Features

- Large masses within cystic lesion connected to dilated main pancreatic duct
  - Similar to combined-type IPMN

MACROSCOPIC

General Features

- Usually unilocular or multilocular and cystic with soft red-brown or tan-red papillary masses

Size

- Range: 1.6-15 cm
- Average: 4-6 cm

MICROSCOPIC

Histologic Features

- Architecturally complex intraductal epithelial proliferation with arborizing papillae, cribriforming, and solid nests
  - Often classified as having high-grade dysplasia given architectural complexity
- Neoplastic epithelial cells exhibit abundant granular eosinophilic cytoplasm with large nuclei and prominent nucleoli
- Both intracytoplasmic and intercellular lumina are found, many containing mucin, with scattered goblet cells
- Stroma can be edematous or myxoid at tip &/or base of papillae
- Invasive carcinomas, often minimally invasive, are found in 25-50% of reported cases, and some retain oncocytic features

Immunohistochemistry

- Stain strongly with MUC6
- Variable staining with MUC1, MUC2, MUC5AC, CEA, CA19-9
- May have focal chromogranin, chymotrypsin positivity
- Hepatocyte antigen-positive

DIFFERENTIAL DIAGNOSIS

Other Types of IPMN

- Complex architecture and eosinophilic cytoplasm are distinct from gastric- or intestinal-type epithelium
- Overlap with pancreatobiliary-type IPMN, but abundant granular eosinophilic cytoplasm should be prominent feature in cases designated IOPN

Other Solid Pancreatic Neoplasms

- If solid growth pattern predominates
  - Pancreatic endocrine neoplasm
    - – Diffusely positive for chromogranin, synaptophysin
  - Acinar cell carcinoma
    - – Immunoreactivity to trypsin and chymotrypsin
    - – PAS-D(+) granules may be seen in apical aspect of gland-forming cells
  - Solid-pseudopapillary neoplasm
    - – Typically in young female patients
    - – Mark with CD10, vimentin, and nuclear expression of β - catenin

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Similar to IPMN in many aspects but with prominent oncocytic features

SELECTED REFERENCES

1. Basturk, O, et al. The oncocytic subtype is genetically distinct from other pancreatic intraductal papillary mucinous neoplasm subtypes. *Mod Pathol*. 2016; 29(9):1058–1069.
2. Basturk, O, et al. Preferential expression of MUC6 in oncocytic and pancreatobiliary types of intraductal papillary neoplasms highlights a pyloropancreatic pathway, distinct from the intestinal pathway, in pancreatic carcinogenesis. *Am J Surg Pathol*. 2010; 34(3):364–370.
3. Patel, SA, et al. Genetic analysis of invasive carcinoma arising in intraductal oncocytic papillary neoplasm of the pancreas. *Am J Surg Pathol*. 2002; 26(8):1071–1077.
4. Nobukawa, B, et al. Intraductal oncocytic papillary carcinoma with invasion arising from the accessory pancreatic duct. *Gastrointest Endosc*. 1999; 50(6):864–866.
5. Jyotheeswaran, S, et al. A newly recognized entity: intraductal “oncocytic” papillary neoplasm of the pancreas. *Am J Gastroenterol*. 1998; 93(12):2539–2543.
6. Adsay, NV, et al. Intraductal oncocytic papillary neoplasms of the pancreas. *Am J Surg Pathol*. 1996; 20(8):980–994.

Intraductal Tubulopapillary Neoplasm

KEY FACTS

Terminology

- Solid epithelial neoplasm composed of back-to-back tubular glands and papillae that grows within and obstructs pancreatic ducts
    - No grossly visible mucin

Clinical Issues

- Very rare entity
    - Majority are discovered incidentally
    - Age
    - Range: 36-79 years
    - Average: 59 years
- Presentation
    - Similar to intraductal papillary mucinous neoplasms (IPMNs)
        - Symptomatic cases present with abdominal pain
        - Majority discovered incidentally

Macroscopic

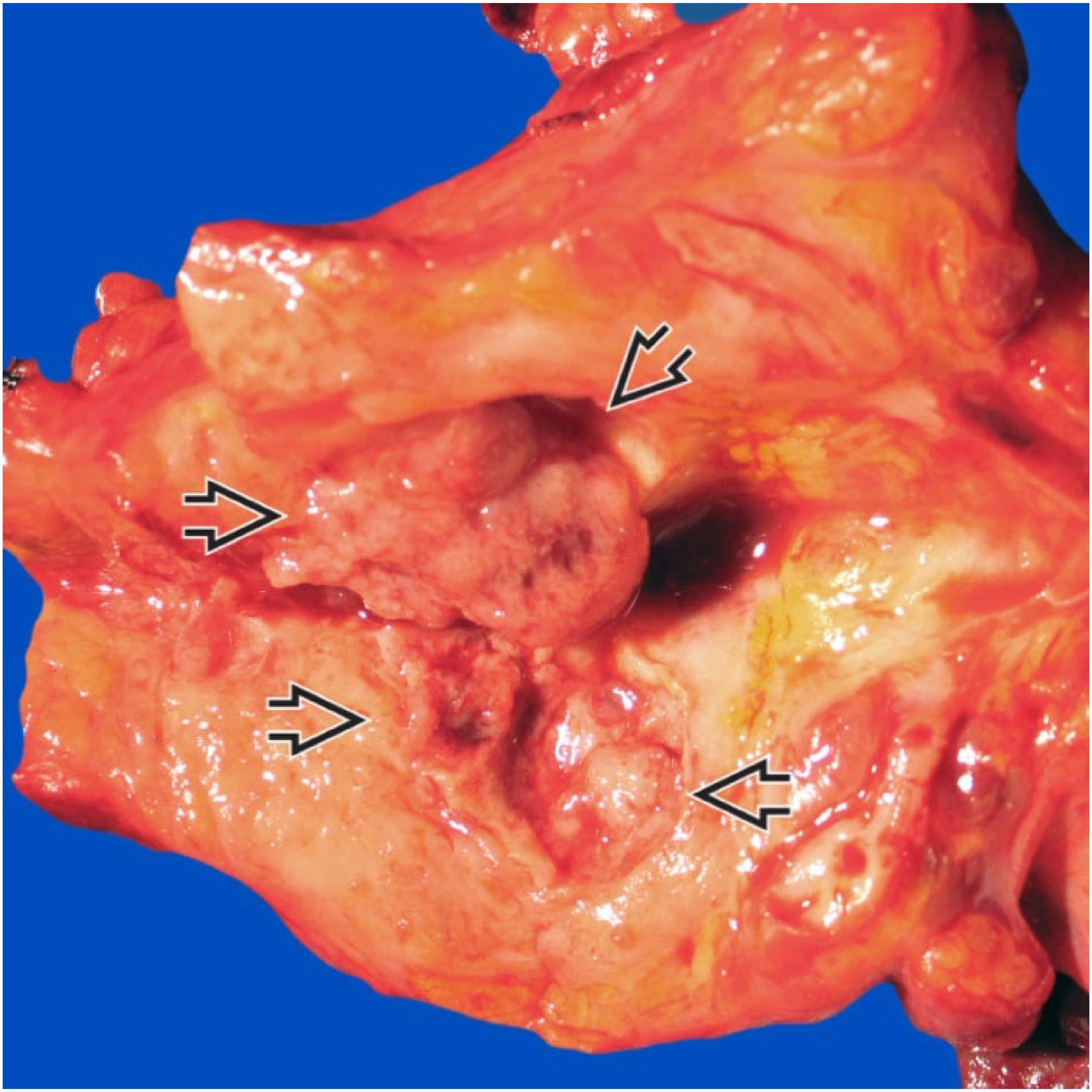
- Size
    - Range: 1-15 cm
    - Average: 4.2 cm

Microscopic

- Tubulopapillary or tubular growth
    - Some may resemble pyloric gland adenomas
    - Scant or absent mucin
- Cases with high-grade dysplasia have marked architectural and cytologic atypia, mitoses, necrosis
- Invasive component may be similar to intraductal component or highly infiltrative

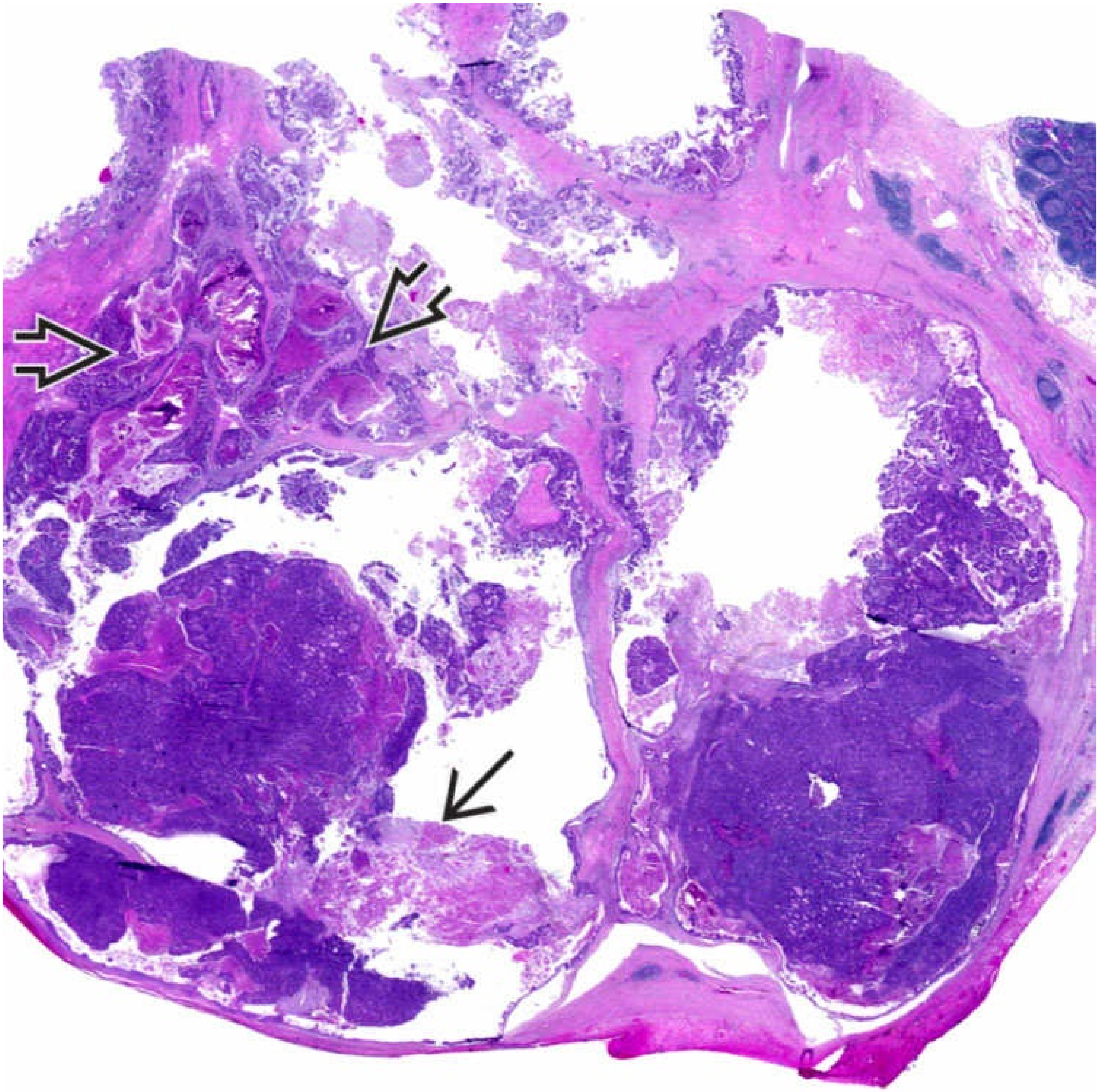
Top Differential Diagnoses

- IPMN
- Acinar cell carcinoma, intraductal variant
- Pancreatic ductal adenocarcinoma



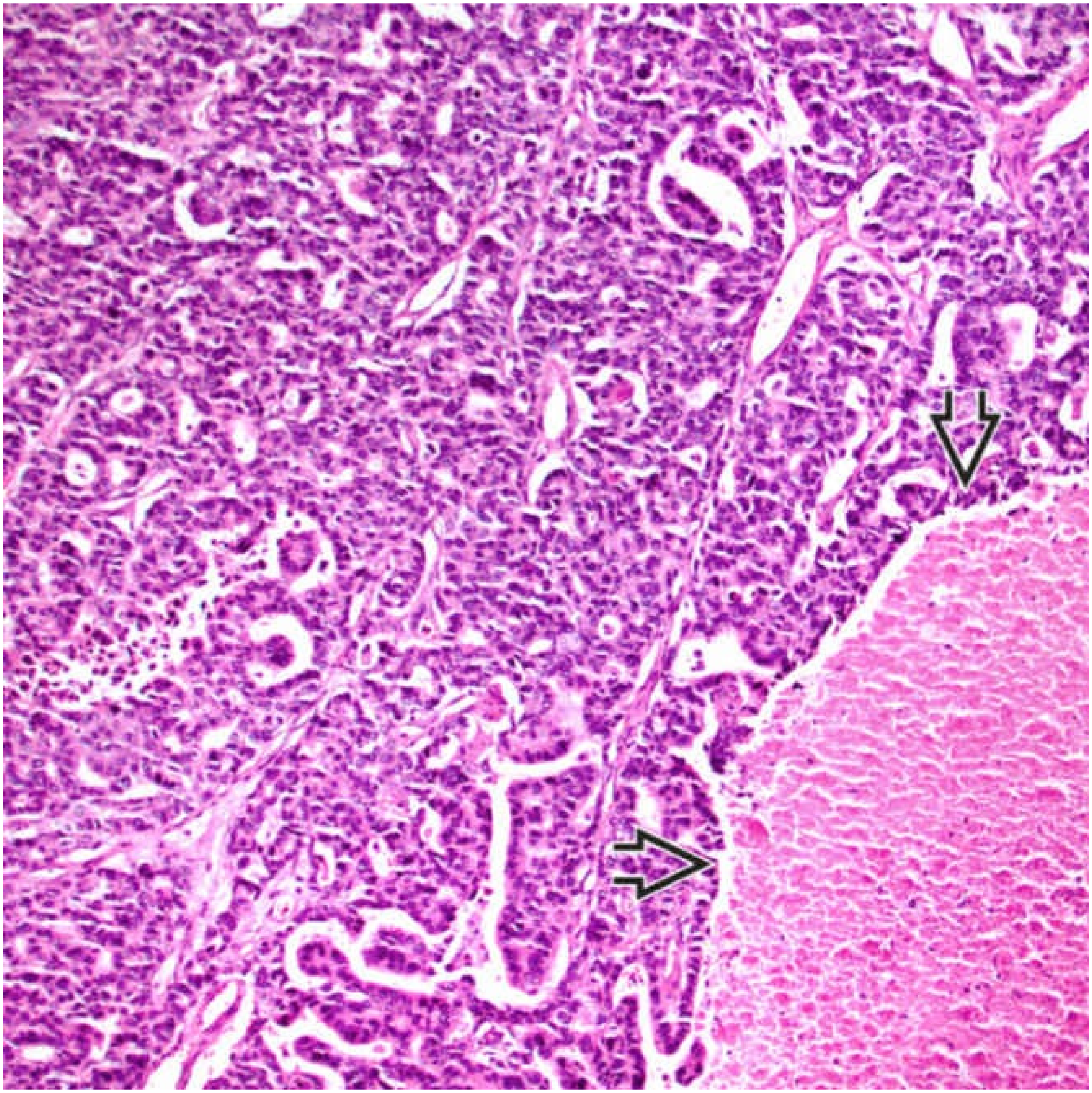
Gross Appearance

This intraductal tubulopapillary neoplasm (ITPN) is forming solid nodules ➩ that obstruct the dilated pancreatic duct. There is no grossly visible mucin.

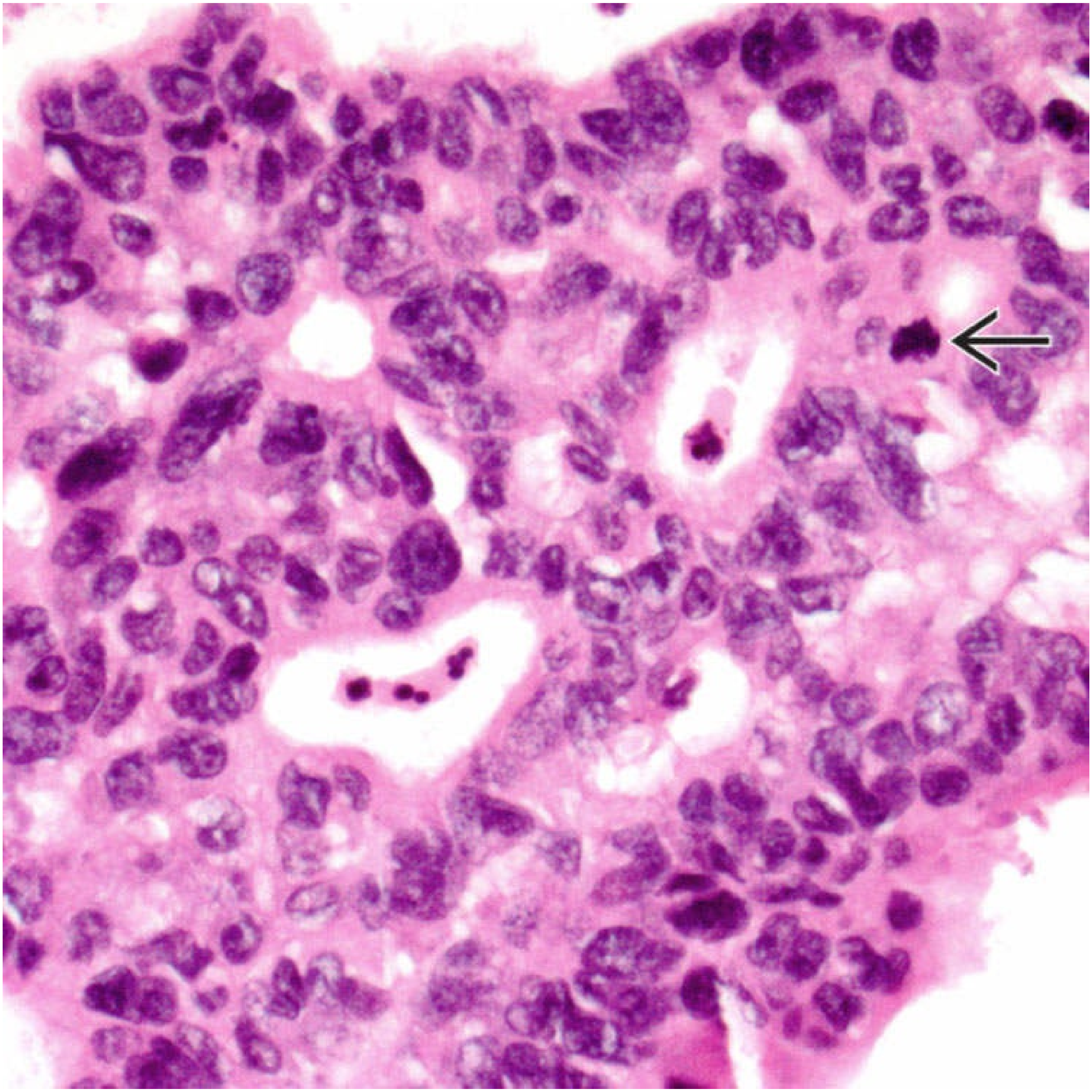


Low-Power View

This low-power view shows an ITPN with stromal invasion. Note the solid masses with focal necrosis → within a dilated duct. A focus of invasion is also seen ⇨ .



Tubulopapillary Growth Pattern
ITPN typically exhibits a cellular, tubulopapillary growth pattern with high-grade cytologic atypia and easily identifiable necrosis .



Back-to-Back Tubules
ITPNs may contain back-to-back tubules. The neoplastic cells have eosinophilic cytoplasm and enlarged, irregular nuclei with scattered mitoses →. There is no mucinous epithelium.

TERMINOLOGY

Abbreviations

- Intraductal tubulopapillary neoplasm (ITPN)
- Intraductal tubular carcinoma (ITC)
- Intraductal tubular adenoma (ITA)
- Intraductal papillary mucinous neoplasm (IPMN)

Definitions

- ITPN: Solid epithelial neoplasm composed of back-to-back tubular glands and papillae that grows within and obstructs pancreatic ducts
  - No visible mucin
- Some authorities group ITC and ITA together as separate diagnostic classification known as intraductal tubular neoplasms
- Others group ITC and ITPN together but classify ITA as pyloric-type IPMN

CLINICAL ISSUES

Epidemiology

- Incidence
  - Rare entity (< 20 cases reported in literature)
- Age
  - Range: 36-79 years
  - Average: 59 years
- Sex
  - Equal sex distribution

Presentation

- Similar to IPMNs
  - Symptomatic cases present with abdominal pain
  - Majority discovered incidentally

Treatment

- Surgical approaches
  - Pancreatectomy with curative intent is treatment of choice

Prognosis

- Limited follow-up data suggest relatively indolent course, especially if no invasive component

MACROSCOPIC

General Features

- Solid nodules obstructing dilated pancreatic ducts
  - Sessile or pedunculated
  - No visible mucin

Size

- Range: 1-15 cm
- Average: 4.2 cm

MICROSCOPIC

Histologic Features

- Tubulopapillary (ITPN) or tubular (ITC, ITA) growth patterns
  - Closely packed glands may resemble pyloric gland adenomas
  - Cuboidal to columnar cells with enlarged nuclei and eosinophilic to amphophilic cytoplasm
- Solid &/or cribriform areas may be seen in some cases
- Scarce or absent cytoplasmic mucin
- May have low- or high-grade dysplasia
  - Cases with high-grade dysplasia have unequivocal architectural and cytologic evidence of malignancy, abundant mitoses, and necrosis
- Invasive component, if present, may resemble intraductal components (tubulopapillary pattern) or may be composed of infiltrating ducts

ANCILLARY TESTS

Immunohistochemistry

- CK7 and CK19 positive; CK20 negative
- Focal MUC1 positivity
- Variable marking with MUC6
- ITA (a.k.a. pyloric gland-type IPMN) is MUC5AC positive; ITPN and ITC are MUC5AC negative
- Markers for pancreatic acinar differentiation, such as trypsin and chymotrypsin, are negative

DIFFERENTIAL DIAGNOSIS

Intraductal Papillary Mucinous Neoplasm

- Dilated pancreatic ducts filled with mucin grossly
- Tall, columnar epithelium with obvious cytoplasmic mucin
- Well-developed papillae with no necrosis
- Consistent marking with MUC5AC

Acinar Cell Carcinoma, Intraductal Variant

- Usually positive for exocrine markers, including trypsin
- Solid nesting pattern with granular cytoplasm

Pancreatic Ductal Adenocarcinoma

- Does not have prominent intraductal growth pattern
- Very infiltrative and destructive
- Marked desmoplastic stroma
- Transition to normal ductal epithelium may help confirm intraductal location of ITC

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Intraductal growth is similar to IPMNs, but lack of mucin and presence of tubulopapillary patterns is distinct from IPMN
- Important to note intraductal growth pattern grossly

SELECTED REFERENCES

1. Chetty, R, et al. Intraductal tubular adenoma (pyloric gland-type) of the pancreas: a reappraisal and possible relationship with gastric-type intraductal papillary mucinous neoplasm. *Histopathology*. 2009; 55(3):270–276.
2. Yamaguchi, H, et al. Intraductal tubulopapillary neoplasms of the pancreas distinct from pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. *Am J Surg Pathol*. 2009; 33(8):1164–1172.
3. Königsrainer, I, et al. Intraductal and cystic tubulopapillary adenocarcinoma of the pancreas–a possible variant of intraductal tubular carcinoma. *Pancreas*. 2008; 36(1):92–95.
4. Tajiri, T, et al. Intraductal tubular neoplasms of the pancreas: histogenesis and differentiation. *Pancreas*. 2005; 30(2):115–121.
5. Albores-Saavedra, J, et al. Intraductal tubular adenoma, pyloric type, of the pancreas: additional observations on a new type of pancreatic neoplasm. *Am J Surg Pathol*. 2004; 28(2):233–238.

Acinar Cell Carcinoma

KEY FACTS

Terminology

- Rare, highly aggressive malignant exocrine carcinoma with acinar differentiation

Clinical Issues

- 1-2% of primary pancreatic neoplasms
  - 5th and 7th decades of life (mean: 58 years)
  - Highly aggressive tumor with high rate of recurrence
  - Minority of patients have associated lipase hypersecretion paraneoplastic syndrome

Macroscopic

- Solid, well-circumscribed, fleshy mass
- Average 10 cm in diameter (range: 2-30 cm)

Microscopic

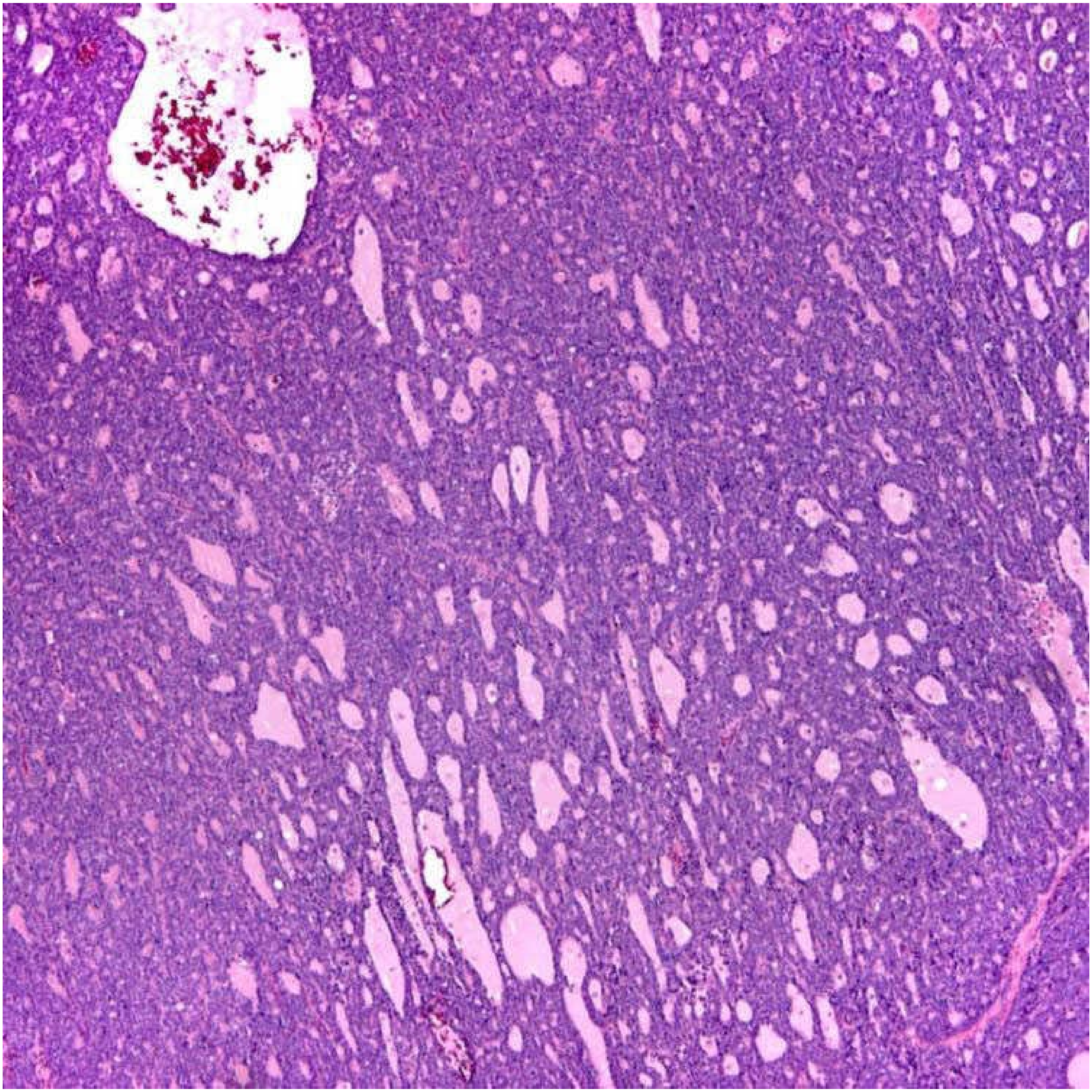
- Densely cellular with multiple architectural patterns, most commonly acinar or solid
  - Uniform nuclei with central prominent nucleolus
  - Eosinophilic, finely granular cytoplasm
- Minimal to moderate finely granular, eosinophilic to amphophilic cytoplasm
- Typically have minimal stroma

Ancillary Tests

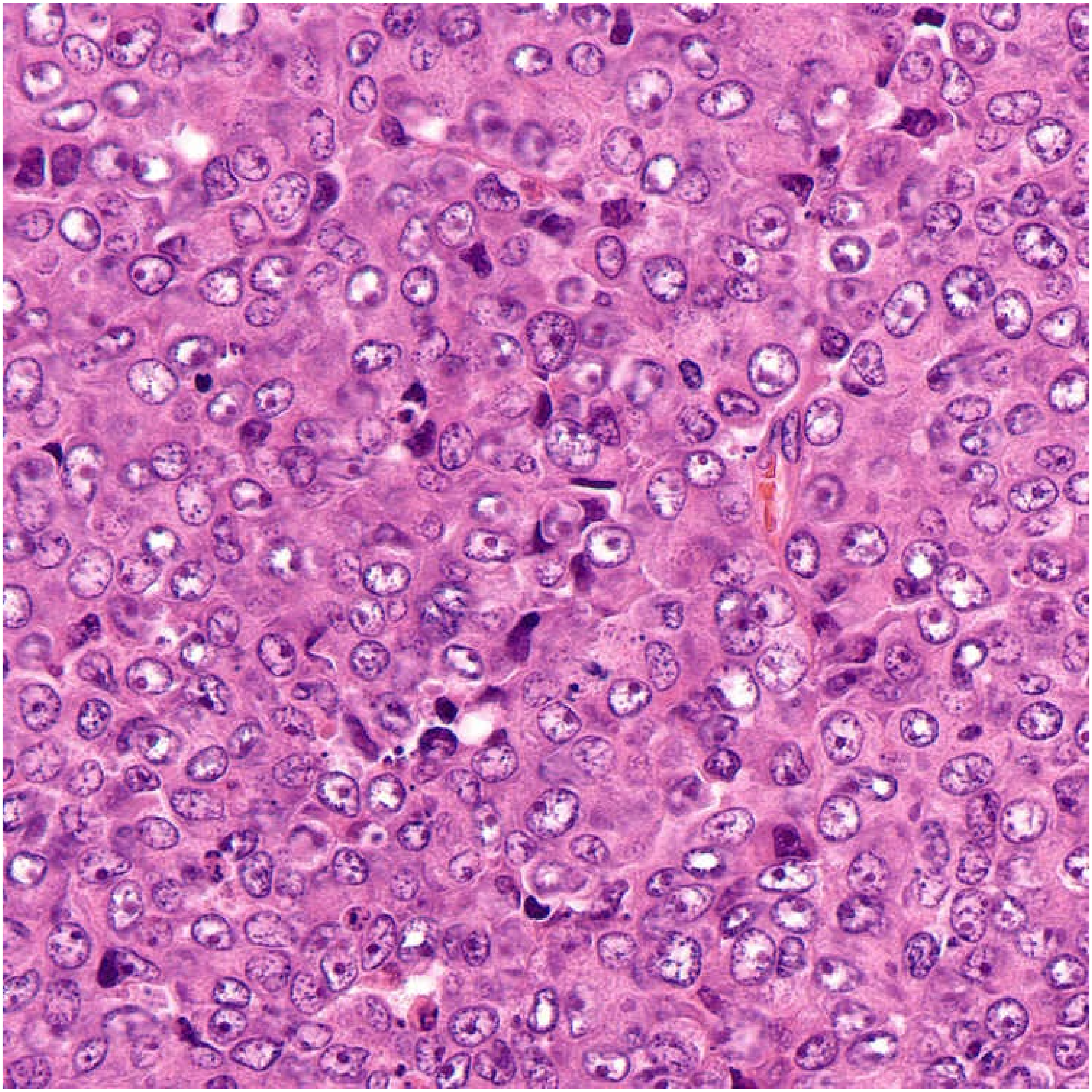
- Immunohistochemistry
  - Pancreatic exocrine enzymes: Trypsin (97%), chymotrypsin (66-95%), and lipase (70-84%)
  - Cytokeratin 8 and 18
  - Focal staining for synaptophysin or chromogranin (35-54%), which may cause confusion with neuroendocrine neoplasms
- PAS positive, resistant to diastase digestion

  - Many have insufficient quantities of zymogen granules, resulting in negative stain
- Genetic alterations
  - Alterations in APC/β-catenin pathway (24% of ACC)
  - Allelic loss of chromosome arm 11p (50% of ACC)

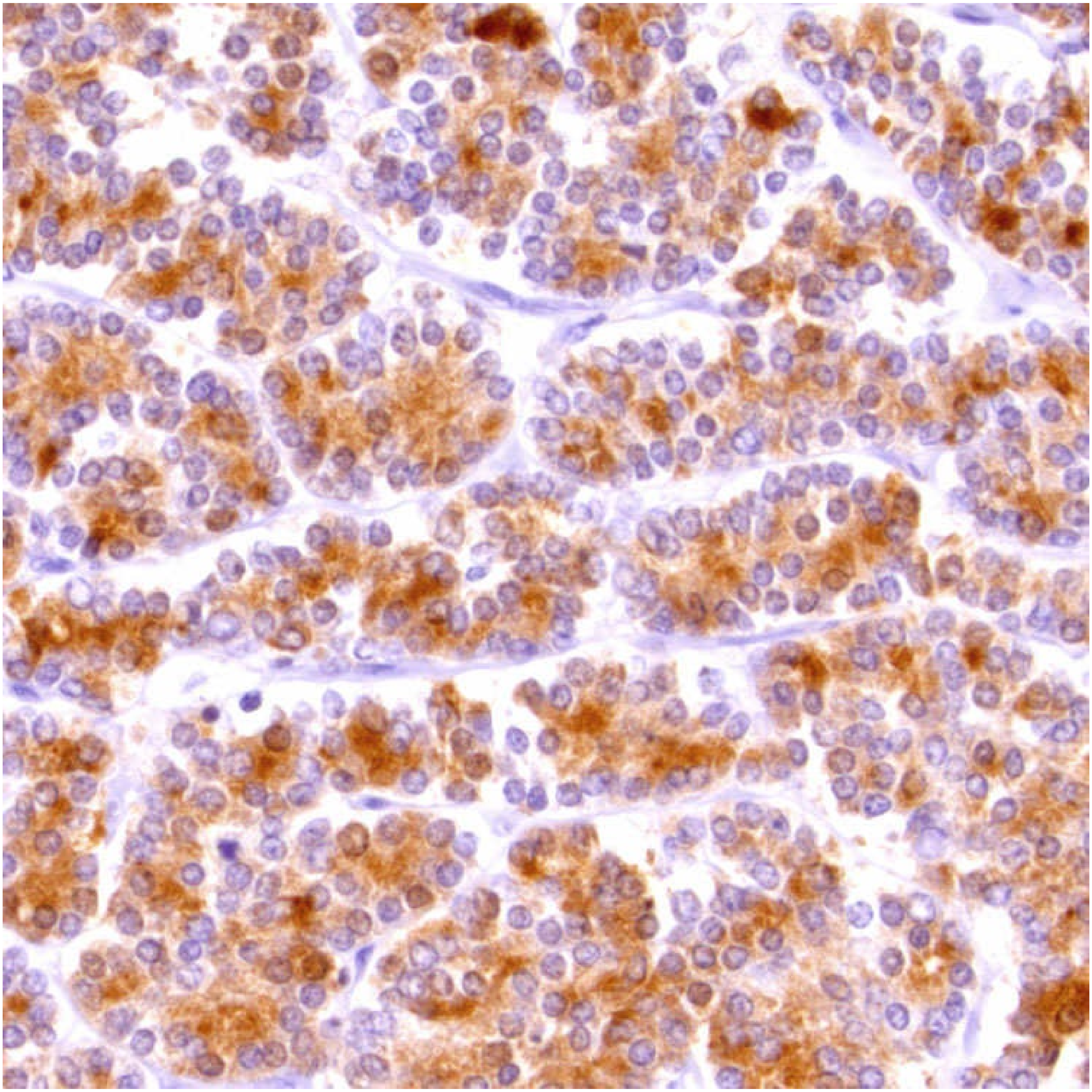
Gross Specimen
This relatively well-circumscribed acinar cell carcinoma (ACC) is large, fleshy, and white-tan with a lobular configuration and easily identifiable necrosis.



Acinar and Glandular Patterns With Minimal Stroma
At low power, ACCs are densely cellular and typically have a relatively small or no significant stromal component. Note the well-formed acinar and glandular patterns.



Nuclear Features
This ACC with a solid growth pattern shows solid sheets of neoplastic cells with relatively uniform nuclei featuring vesicular chromatin, characteristic prominent nucleoli, and eosinophilic cytoplasm.



Acinar Cell Carcinoma, Immunohistochemistry
Antibodies against pancreatic exocrine enzymes are the most sensitive marker of ACC. Note the cytoplasmic staining for trypsin. Chymotrypsin can be equally beneficial, and lipase is detected slightly less often.

TERMINOLOGY

Abbreviations

- Acinar cell carcinoma (ACC)

Definitions

- Malignant exocrine carcinoma with acinar differentiation

- Produces pancreatic exocrine enzymes in zymogen granules

CLINICAL ISSUES

Epidemiology

- Incidence
  - 1-2% of primary pancreatic neoplasms
- Age
  - Between 5th and 7th decades of life (mean: 58 years)
  - Rare in children
- Sex
  - Male predominance

Presentation

- Nonspecific symptoms (abdominal pain, weight loss)
  - Associated with lipase hypersecretion paraneoplastic syndrome (10-15%)
  - Subcutaneous fat necrosis and polyarthralgia

Laboratory Tests

- Elevated serum lipase in lipase hypersecretion syndrome
- Elevated α-fetoprotein in younger patients

Treatment

- Surgical resection and adjuvant therapy

Prognosis

- Highly aggressive tumor with high rate of recurrence
  - Most patients have metastatic disease at presentation, usually to lymph nodes and liver
- Overall 5-year survival is 6%

MACROSCOPIC

General Features

- Solid, circumscribed mass; capsular invasion common
  - Solid, fleshy, lobulated, tan to red cut surface
  - Rare cystic variant with innumerable variably sized cysts (acinar cell cystadenocarcinoma)

Size

- Average of 10 cm in diameter (range: 2-30 cm)

MICROSCOPIC

Histologic Features

- Densely cellular tumor with several architectural patterns
  - Acinar: Minute lumina with basally located nuclei and apical cytoplasm
  - Glandular: Dilated acinar lumens
  - Trabecular: Interlacing ribbons of cells with nuclei oriented toward periphery
  - Solid
  - – Sheets and nests of cells without lumen formation
  - – Basal nuclear palisading along stromal interface
- Typically stroma is minimal with no desmoplastic stromal response
- Cytologic features
  - Uniform nuclei with vesicular chromatin
  - Often single prominent central nucleolus
  - Minimal to moderate finely granular, eosinophilic to amphophilic cytoplasm
- Mitotic rate variable; most have easily identifiable mitoses
- Vascular invasion common
- Variants
  - Cystic growth pattern (acinar cell cystadenocarcinoma)
  - Intraductal or papillocystic growth
    - Can mimic intraductal neoplasm
  - Oncocytic ACC: Abundant eosinophilic cytoplasm, may not mark with trypsin
  - Signet ring or clear cell features

ANCILLARY TESTS

Histochemistry

- Positive for periodic acid-Schiff, resistant to diastase digestion
  - Many ACC have insufficient quantities of zymogen granules, resulting in negative stain

Immunohistochemistry

- Pancreatic exocrine enzymes: Trypsin (97%), chymotrypsin (66-95%), and lipase (70-84%)
- Positive for cytokeratin 8 and 18
- Focal staining for synaptophysin or chromogranin (35-54%)
- Amylase, CK7, CK20, and α-fetoprotein can be positive

DIFFERENTIAL DIAGNOSIS

Pancreatic Endocrine Neoplasm

- Salt and pepper chromatin
- Diffusely, rather than focally, positive for synaptophysin and chromogranin

Mixed Endocrine/Acinar Neoplasm

- Acinar cell differentiation and > 25% endocrine differentiation by immunohistochemistry

Pancreatoblastoma

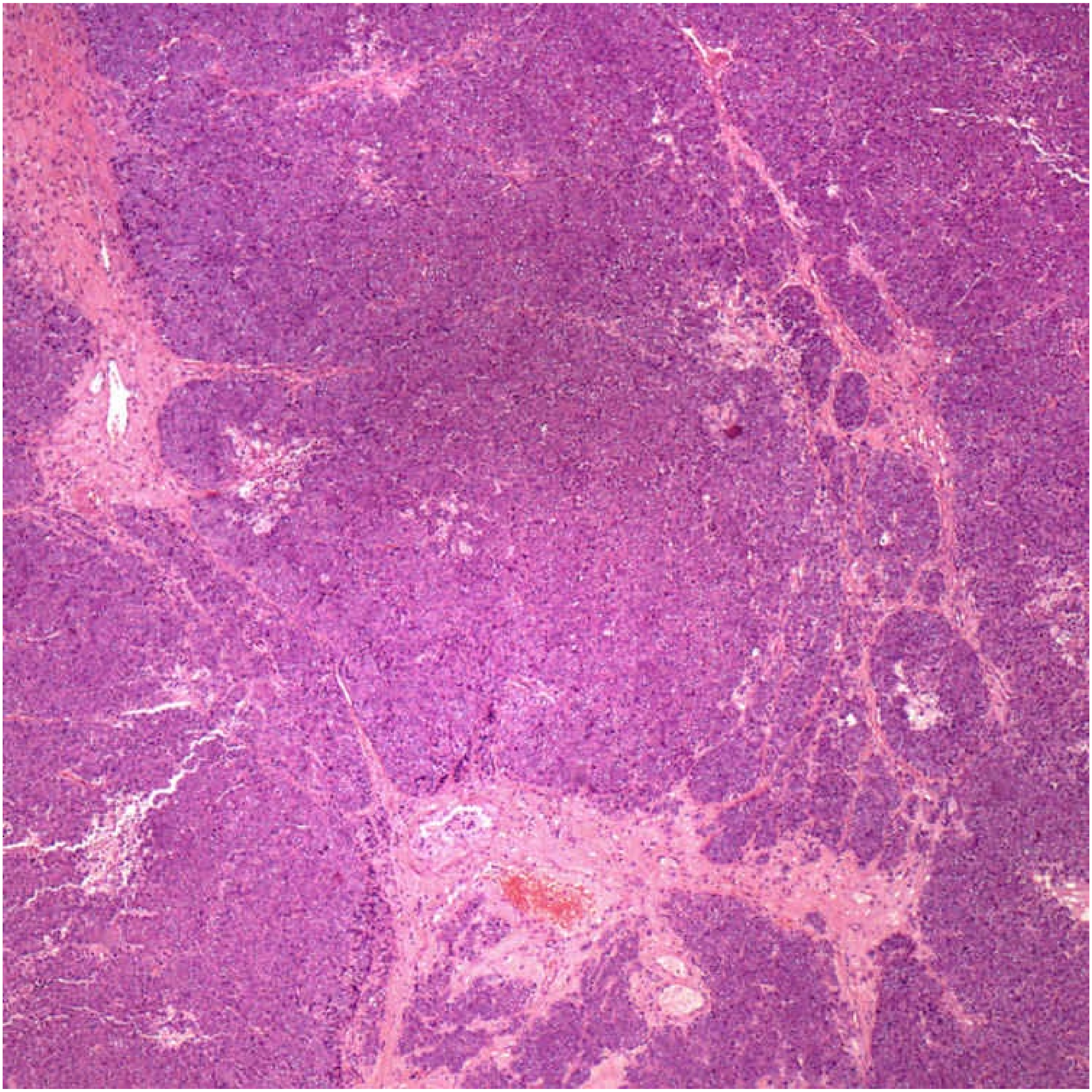
- More common in early childhood; distinctive squamous nests

Solid-Pseudopapillary Neoplasm

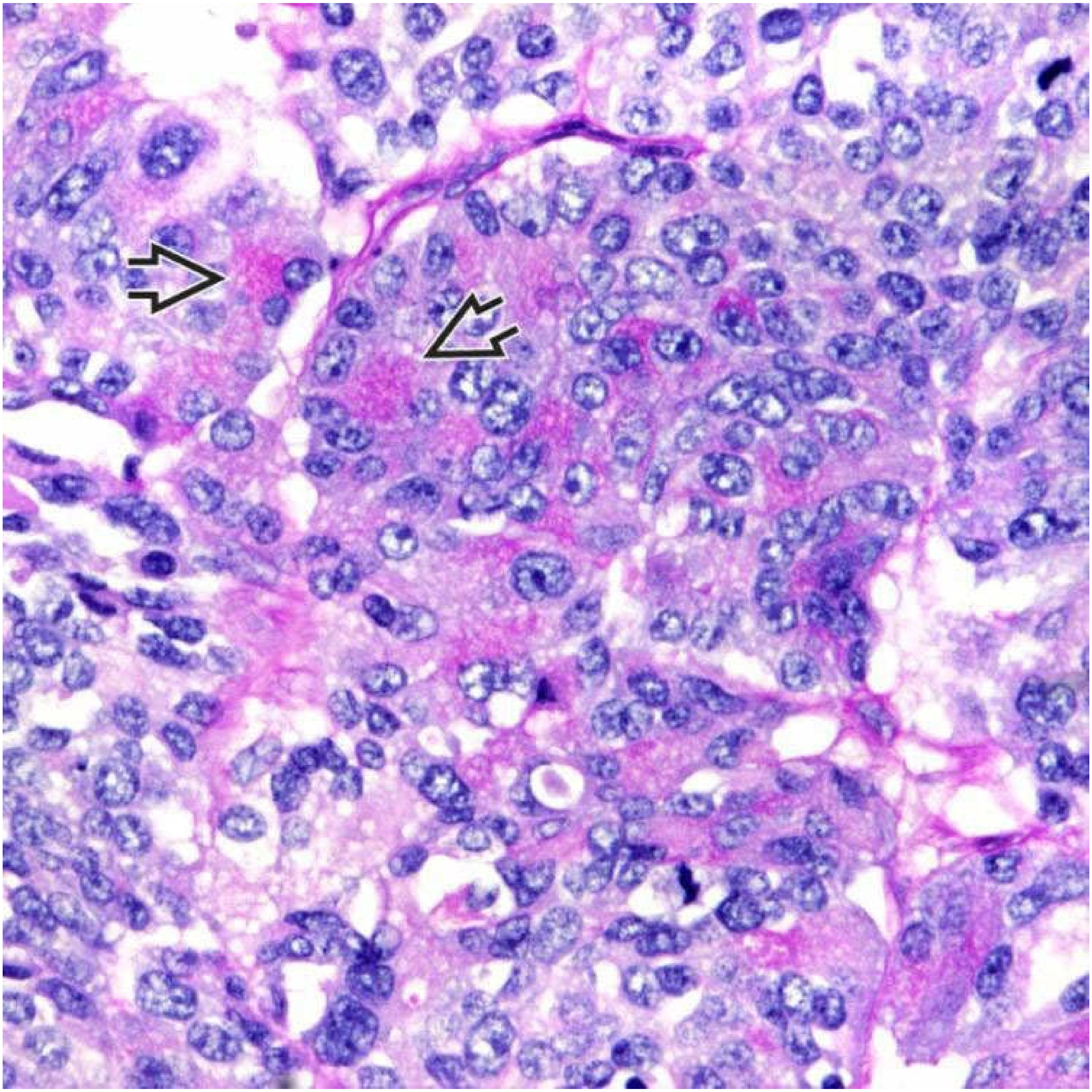
- Characteristic degenerative pseudopapillary formation
- Immunoreactive for β-catenin, not trypsin or chymotrypsin

Acinar Cell Cystadenocarcinoma

This is rare example of a acinar cell cystadenocarcinoma. Note the numerous variably sized cysts on cut section.

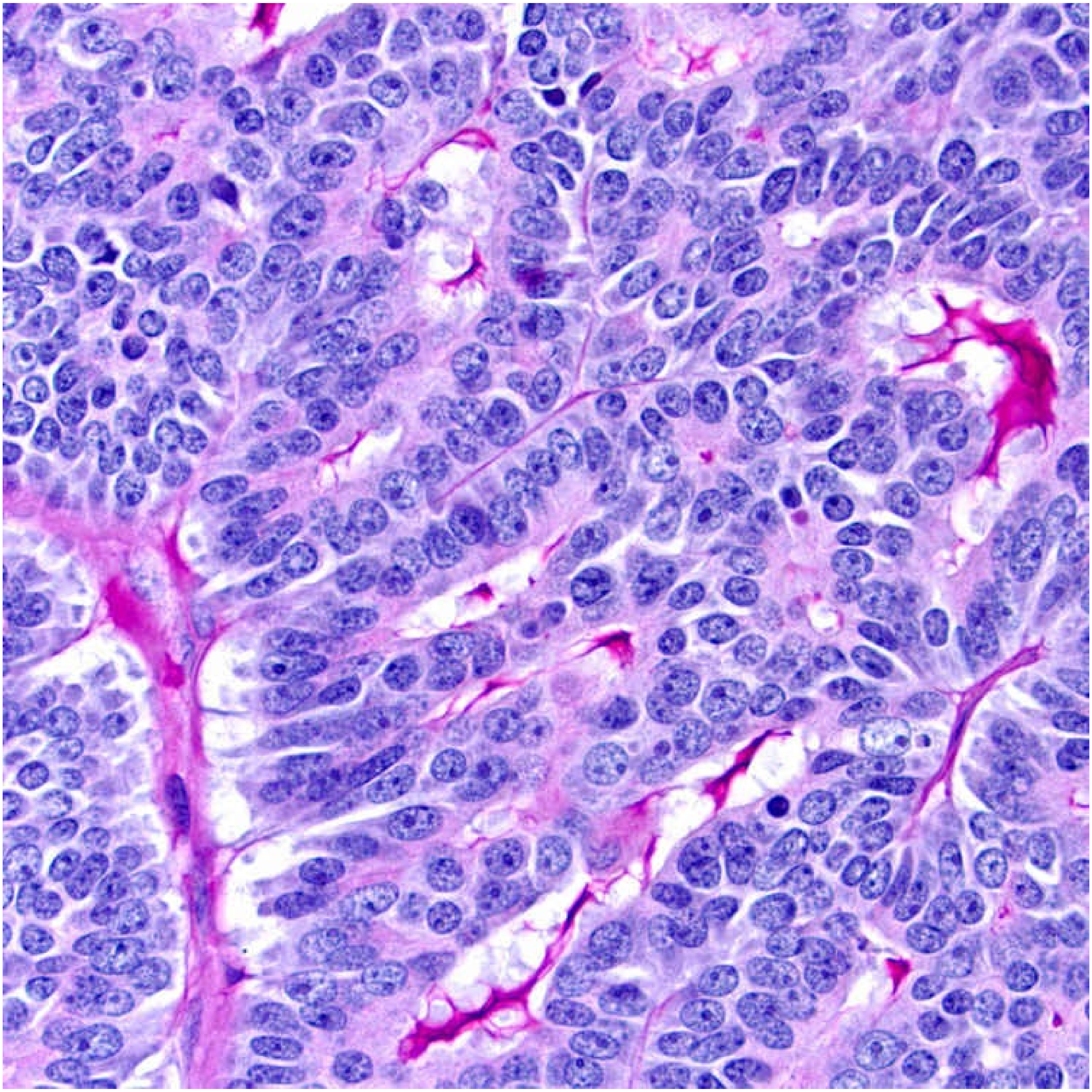


Solid Pattern
This ACC has more stroma than some, but it is still relatively scant compared to the dense cellularity of the tumor. This example has a predominantly solid pattern.



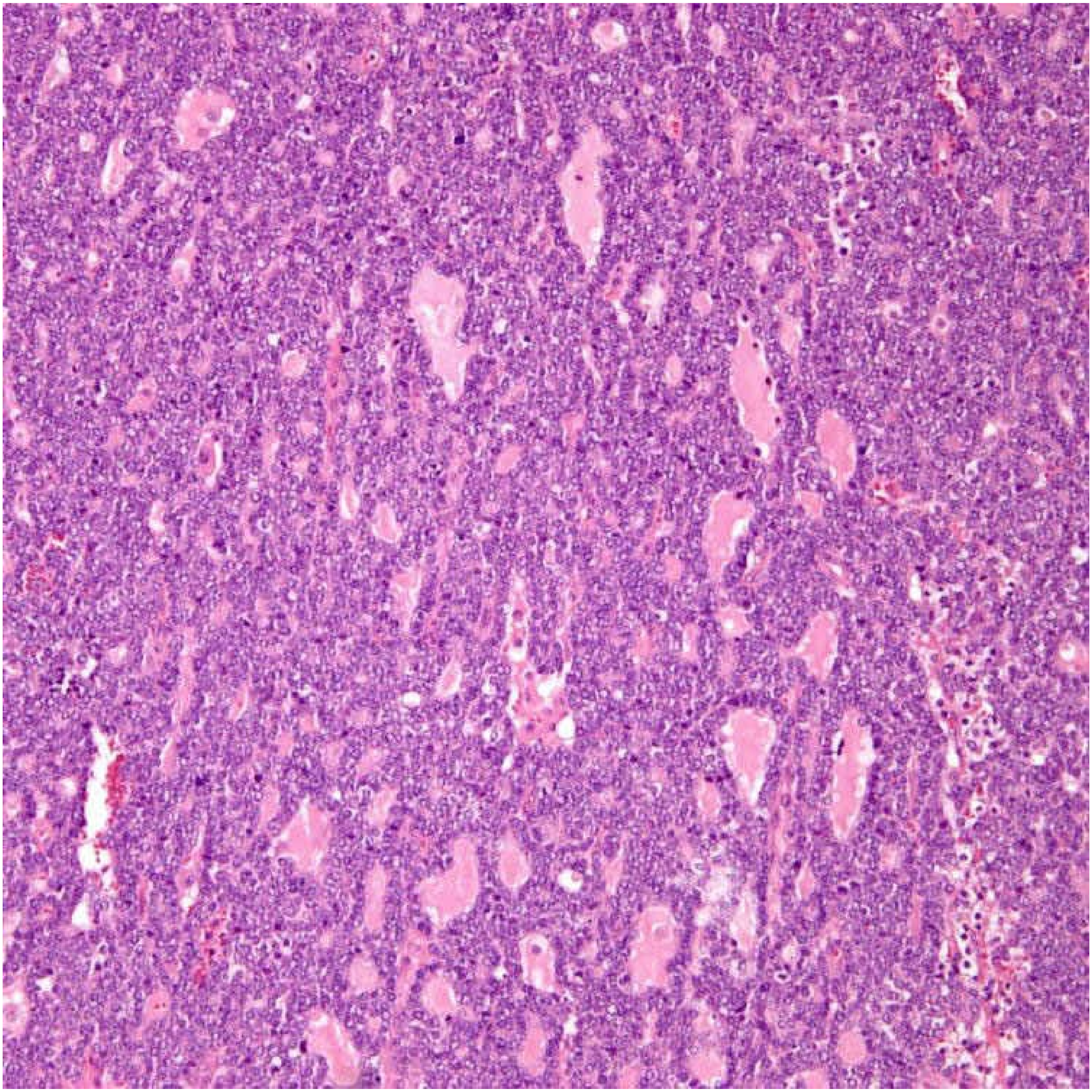
PAS-Diastase

This PAS/diastase highlights very faint granules ⇨ in the cytoplasm of the tumor cells. Note the prominent nucleoli.



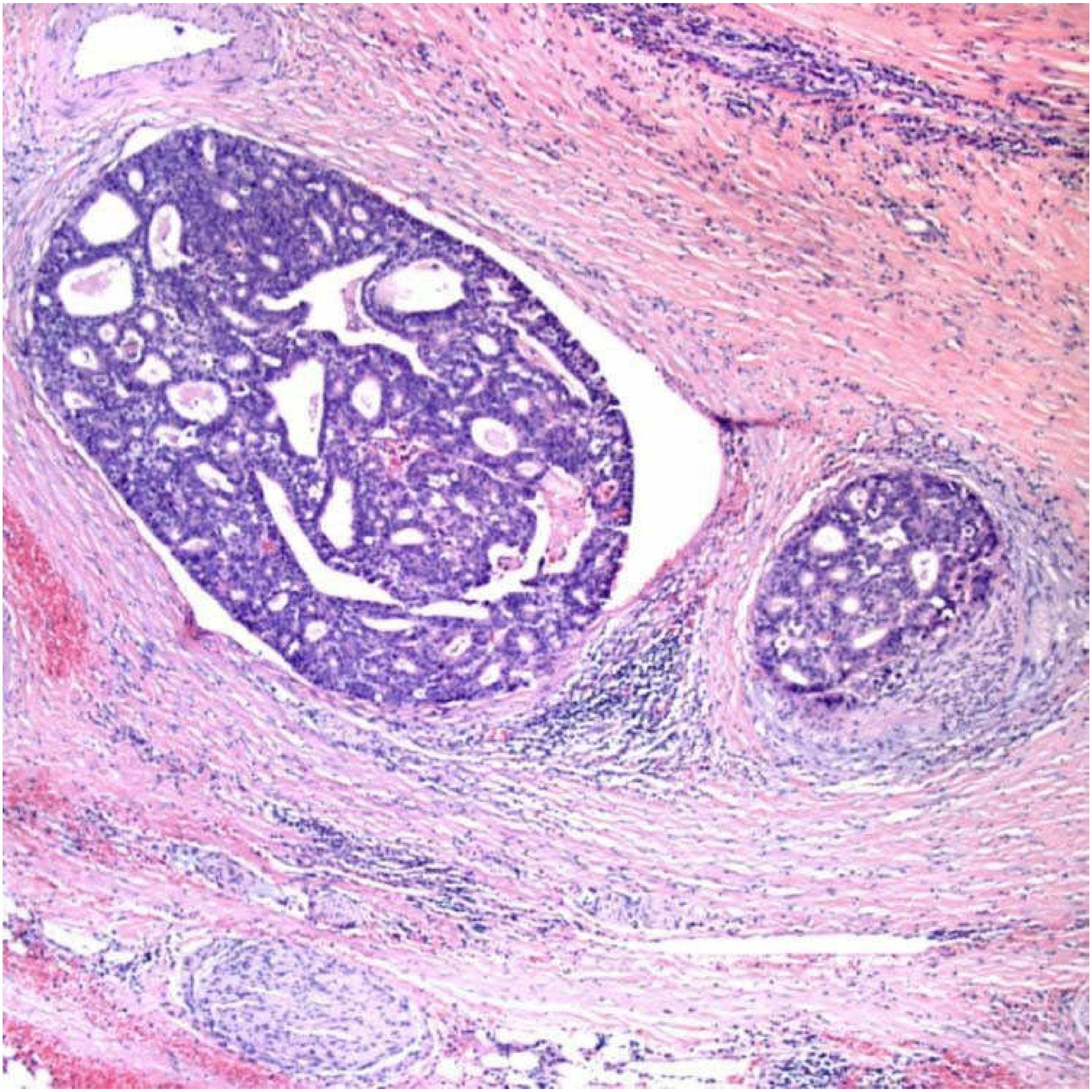
PAS-Diastase

The lack of sufficient cytoplasmic zymogen granules in these neoplastic ACC cells results in a negative PAS/D stain. Note the acinar growth pattern with small lumina and nuclei that are polarized in the acini.

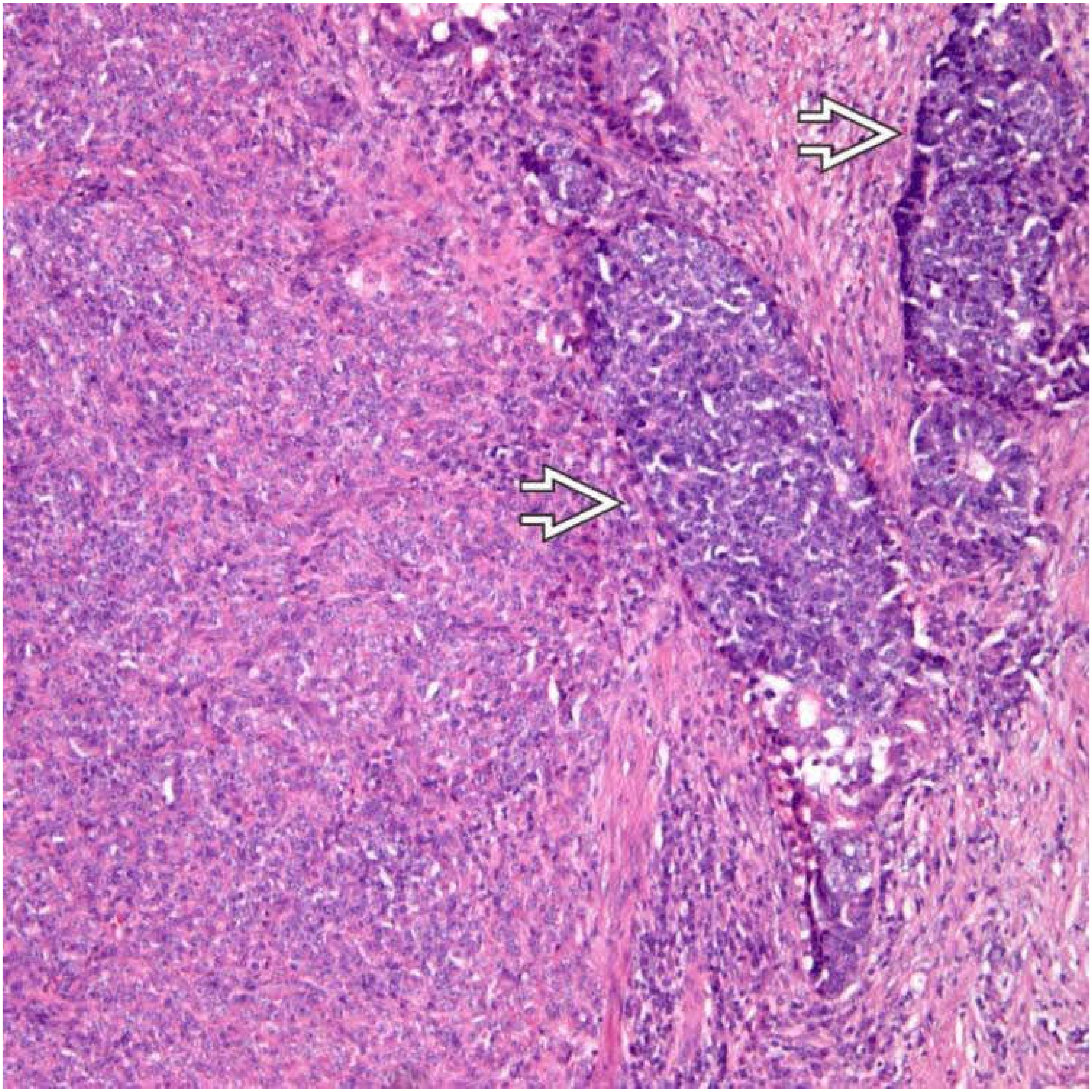


Acinar and Glandular Patterns

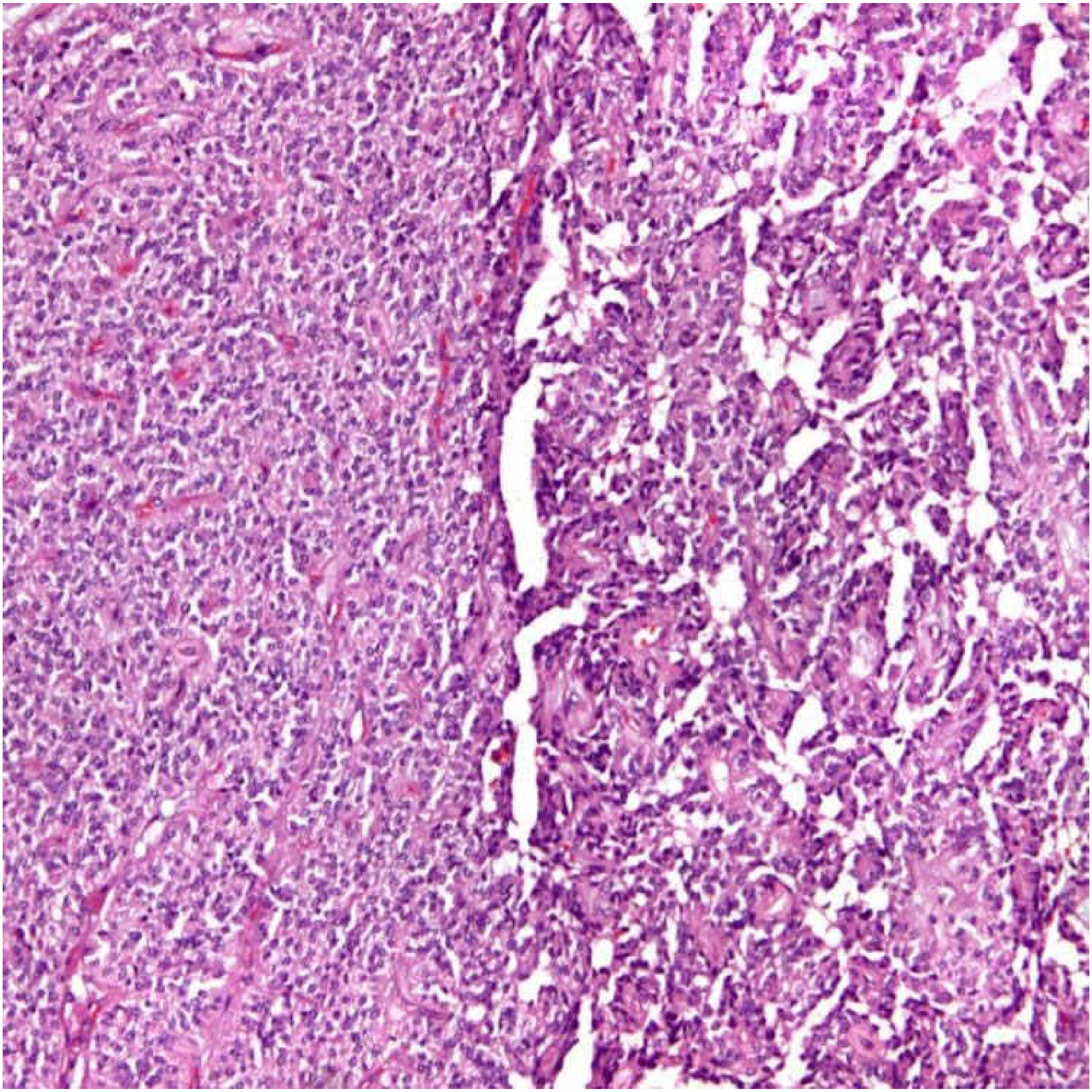
ACC is typically densely cellular. The acinar pattern features minute lumina with basally located nuclei and apical cytoplasm. The glandular pattern is characterized by larger, dilated glandular spaces. This tumor is a mixture of both acinar and glandular patterns. Note that there is essentially no stroma.



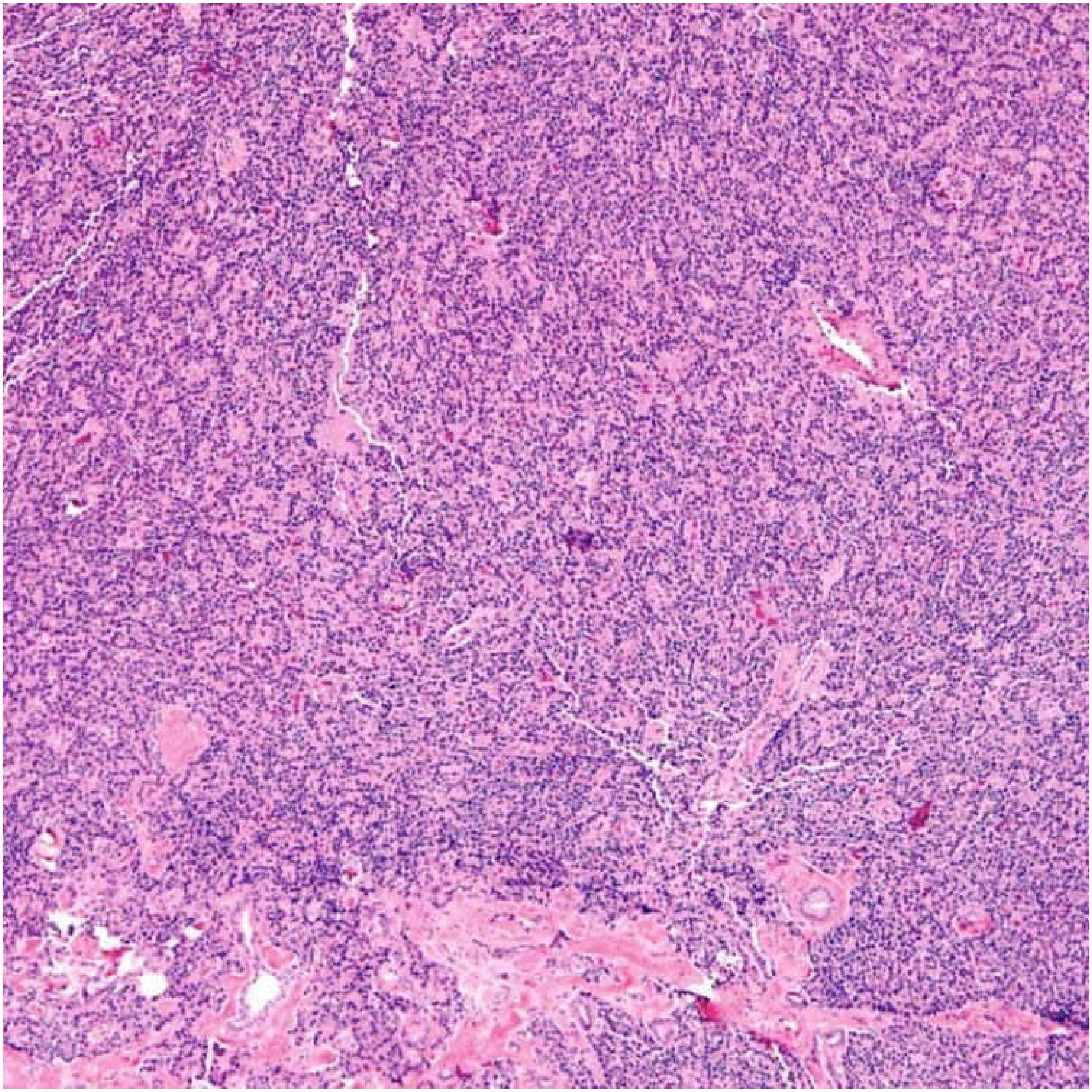
Vascular Invasion
Vascular invasion, as seen here in a large vein, is common in acinar cell carcinoma.



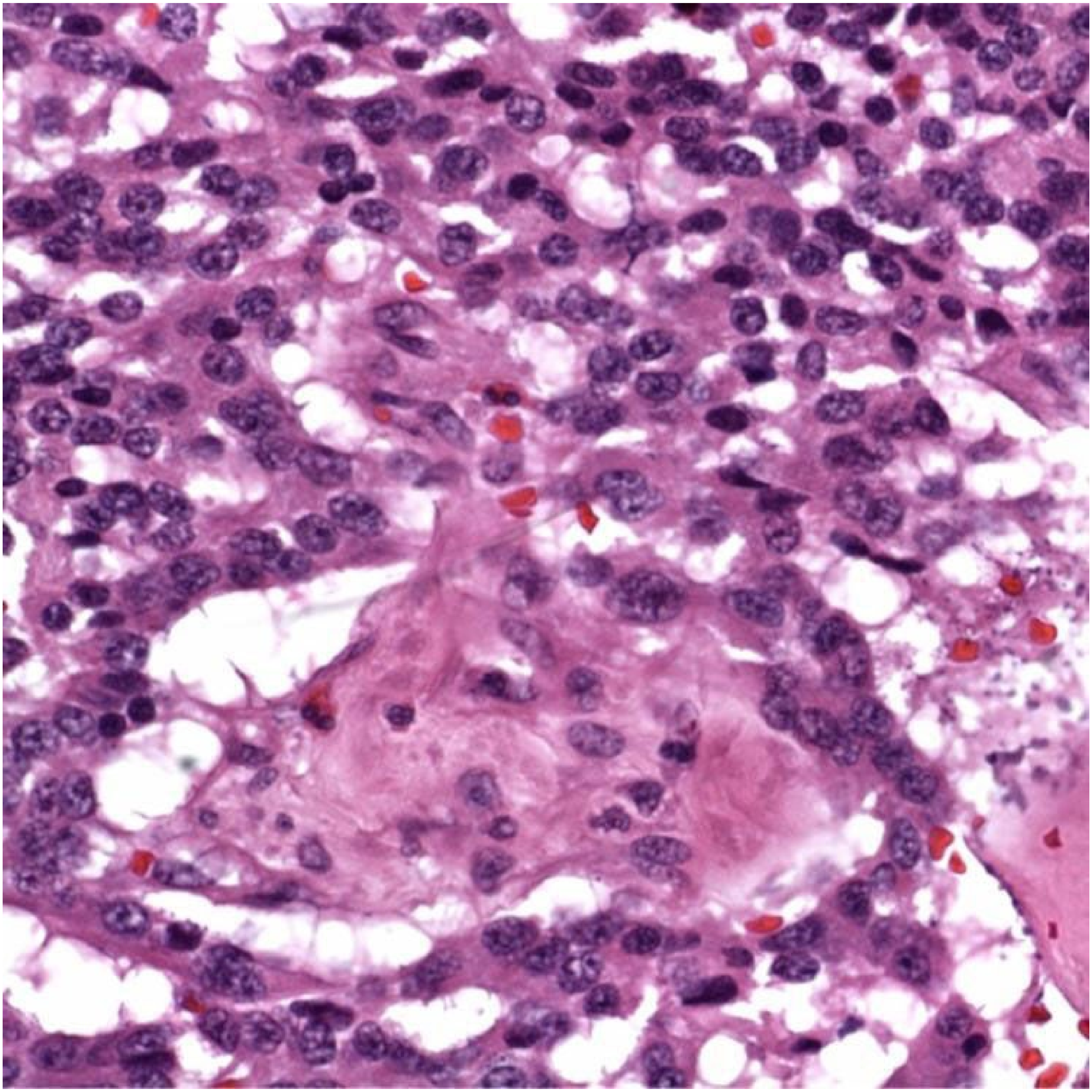
Mixed Acinar Cell Carcinoma/Neuroendocrine Carcinoma
This mixed ACC/neuroendocrine carcinoma shows a solid pattern ACC on the left and neuroendocrine elements on the right. This diagnosis must be confirmed with immunohistochemistry for the neuroendocrine component, which should comprise 25% or more.



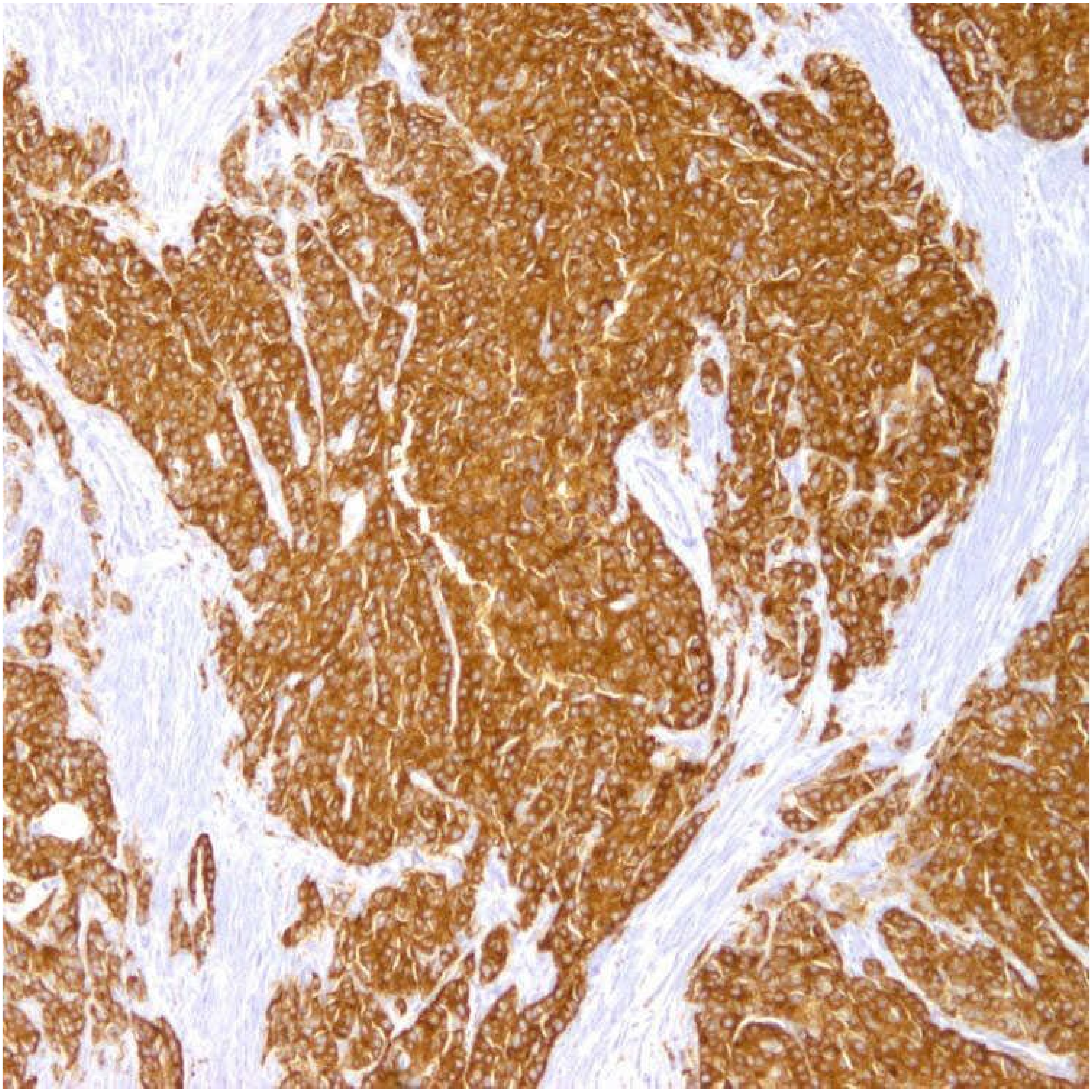
Differential Diagnosis: Solid Pseudopapillary Tumor
Although solid pseudopapillary tumors may have solid &/or acinar growth patterns, the degenerative changes and pseudopapillary areas (seen on the right) help make the distinction from ACC.



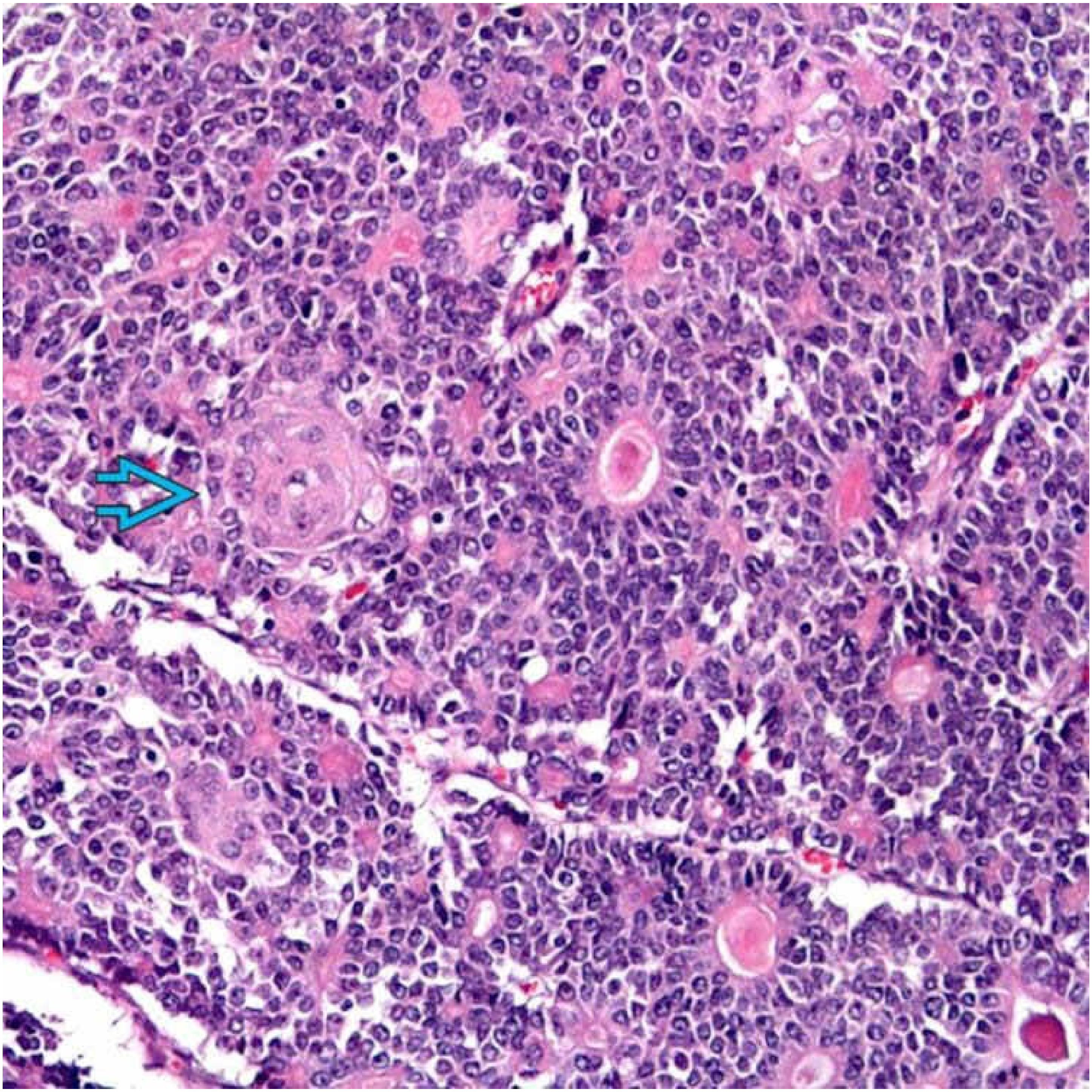
Differential Diagnosis: Well-Differentiated Neuroendocrine Tumor
This low-power view of a well-differentiated pancreatic neuroendocrine tumor shows a solid and acinar growth pattern.



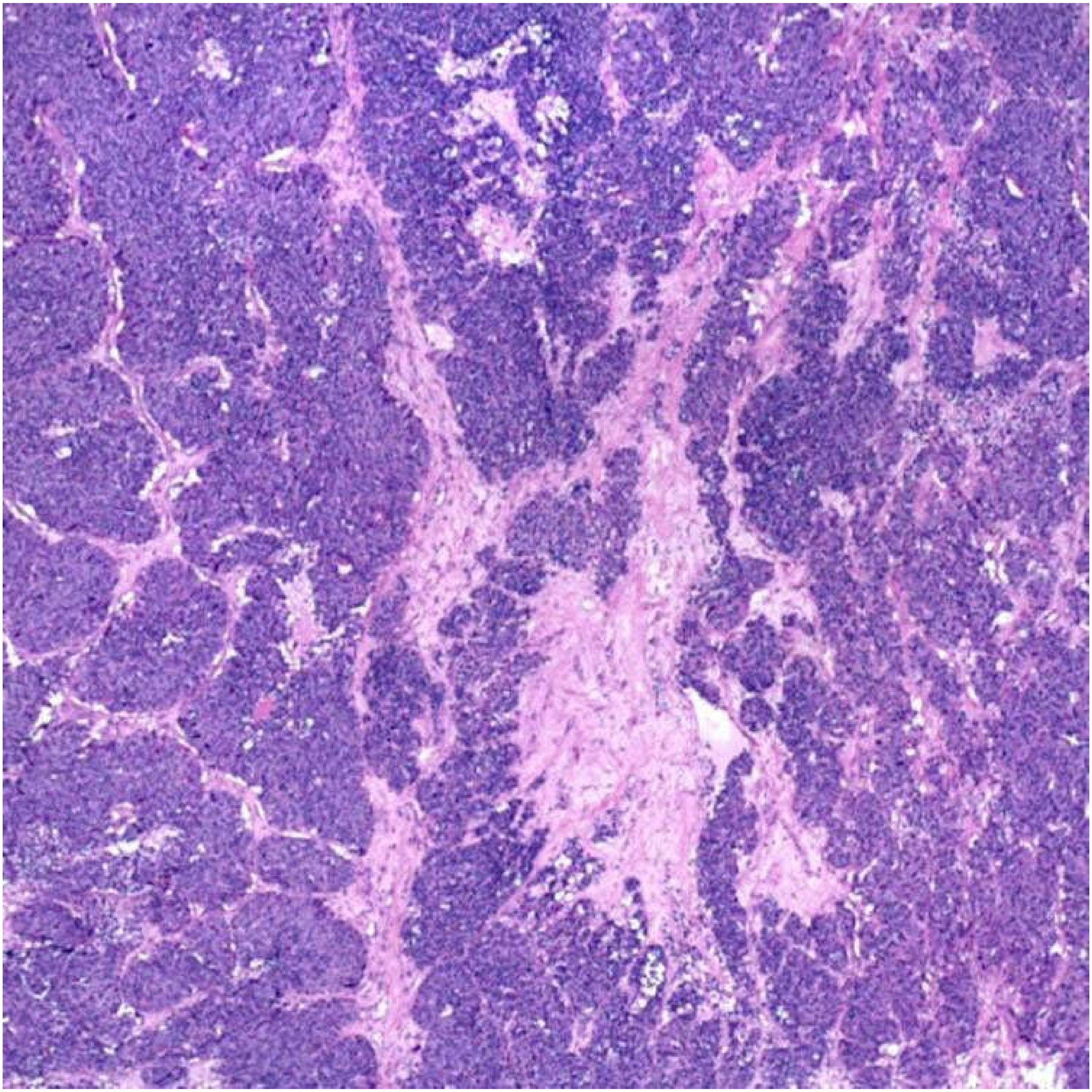
Differential Diagnosis: Well-Differentiated Neuroendocrine Tumor
This well-differentiated neuroendocrine tumor has a solid and acinar growth pattern, but the salt and pepper chromatin pattern of the nuclei are characteristic of a neuroendocrine tumor.



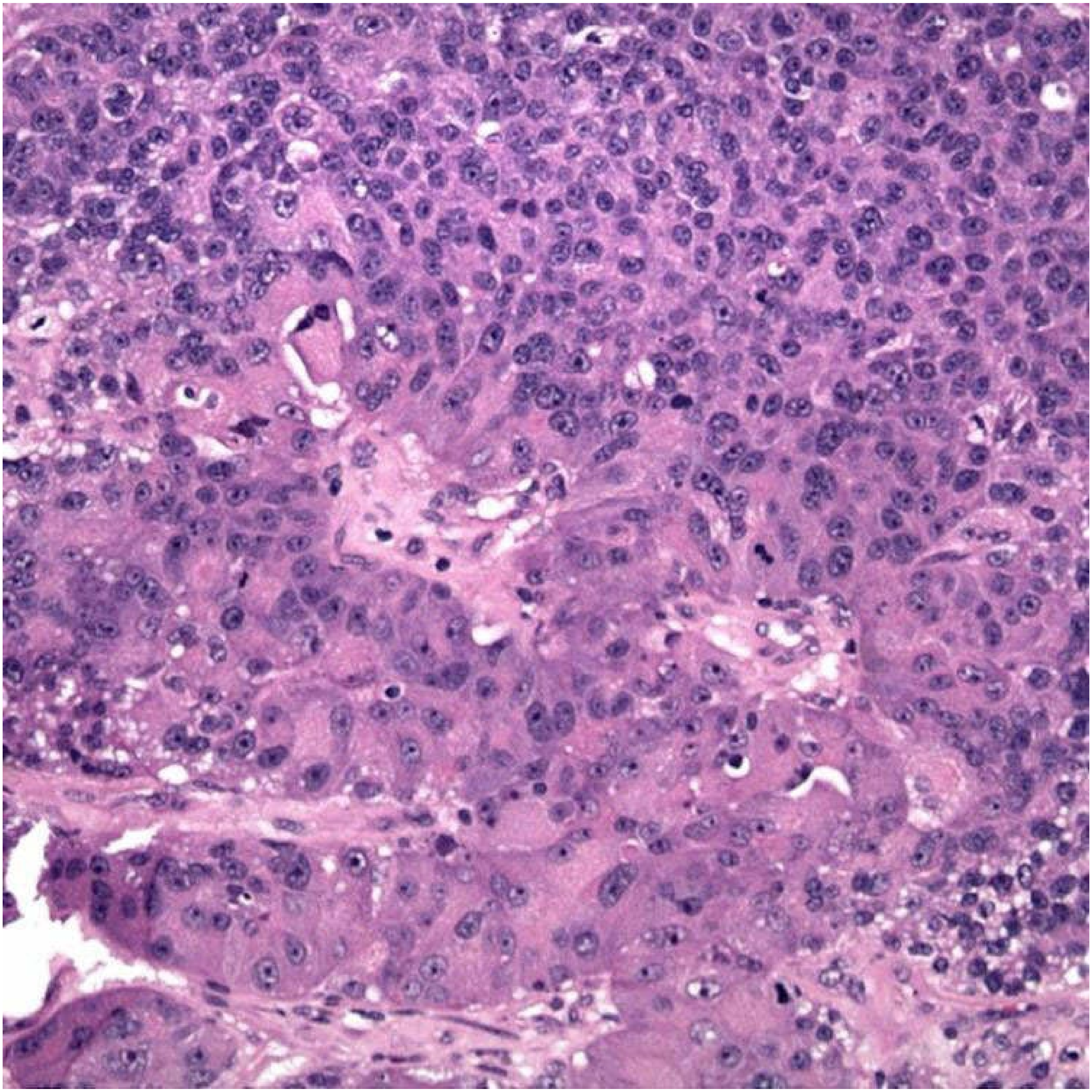
Differential Diagnosis: Neuroendocrine Tumors
Neuroendocrine tumors are strongly and diffusely positive for synaptophysin. ACC can mark with neuroendocrine markers, but it is typically focal.



Differential Diagnosis: Pancreatoblastoma
This pancreatoblastoma has an acinar growth pattern, but the squamoid nests are diagnostic of pancreatoblastoma. This specimen was from a child with an abdominal mass.



This ACC has more stroma than is often seen, but there is no desmoplasia. Note the dense cellularity of the tumor.



This ACC has a solid growth pattern. The nuclei have a single very prominent nucleolus, and there is abundant eosinophilic, finely granular cytoplasm.

SELECTED REFERENCES

1. Stelow, EB, et al. Pancreatic acinar cell carcinomas with prominent ductal differentiation: mixed acinar ductal carcinoma and mixed acinar endocrine ductal carcinoma. *Am J Surg Pathol*. 2010; 34(4):510–518.
2. Matos, JM, et al. Pancreatic acinar cell carcinoma: a multi-institutional study. *J Gastrointest Surg*. 2009; 13(8):1495–1502.
3. Seth, AK, et al. Acinar cell carcinoma of the pancreas: an institutional series of resected patients and review of the current literature. *J Gastrointest Surg*. 2008; 12(6):1061–1067.
4. Basturk, O, et al. Intraductal and papillary variants of acinar cell carcinomas: a new addition to

the challenging differential diagnosis of intraductal neoplasms. *Am J Surg Pathol*. 2007; 31(3):363–370.

5. Klimstra, DS. Nonductal neoplasms of the pancreas. *Mod Pathol*. 2007; 20(Suppl 1):S94–112.
6. Ordóñez, NG, et al. Acinar cell carcinoma of the pancreas. *Ultrastruct Pathol*. 2000; 24(4):227–241.

Pancreatoblastoma

KEY FACTS

Terminology

- Malignant epithelial neoplasm with multiple lines of differentiation
  - Acinar, squamous, endocrine, ductal, or mesenchymal components may be seen
- Many are associated with mutations in β-catenin/ *APC* pathway

Clinical Issues

- Rare overall but most common malignant pancreatic neoplasm of childhood
  - 2/3 of pancreatoblastoma occur in children, 1/3 in adults
  - Mean age at diagnosis is 2.4 years in children and 40 years in adults
- Presents as abdominal mass, often palpable in children, and abdominal pain
  - 25-30% have elevated α-fetoprotein
- Overall survival only 50%
  - Prognosis worse in adults

Macroscopic

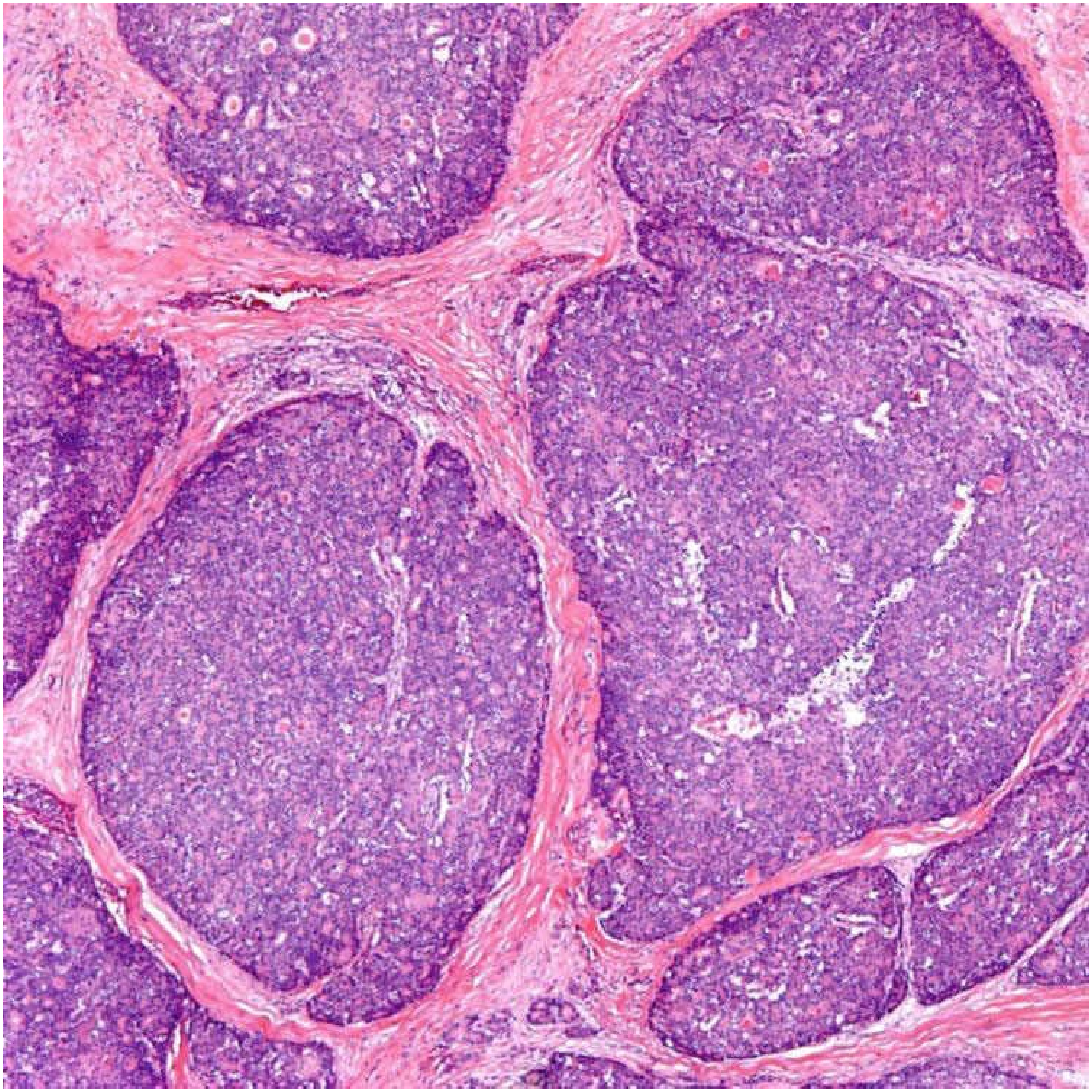
- Usually solitary
- Well circumscribed
- Lobulated

Microscopic

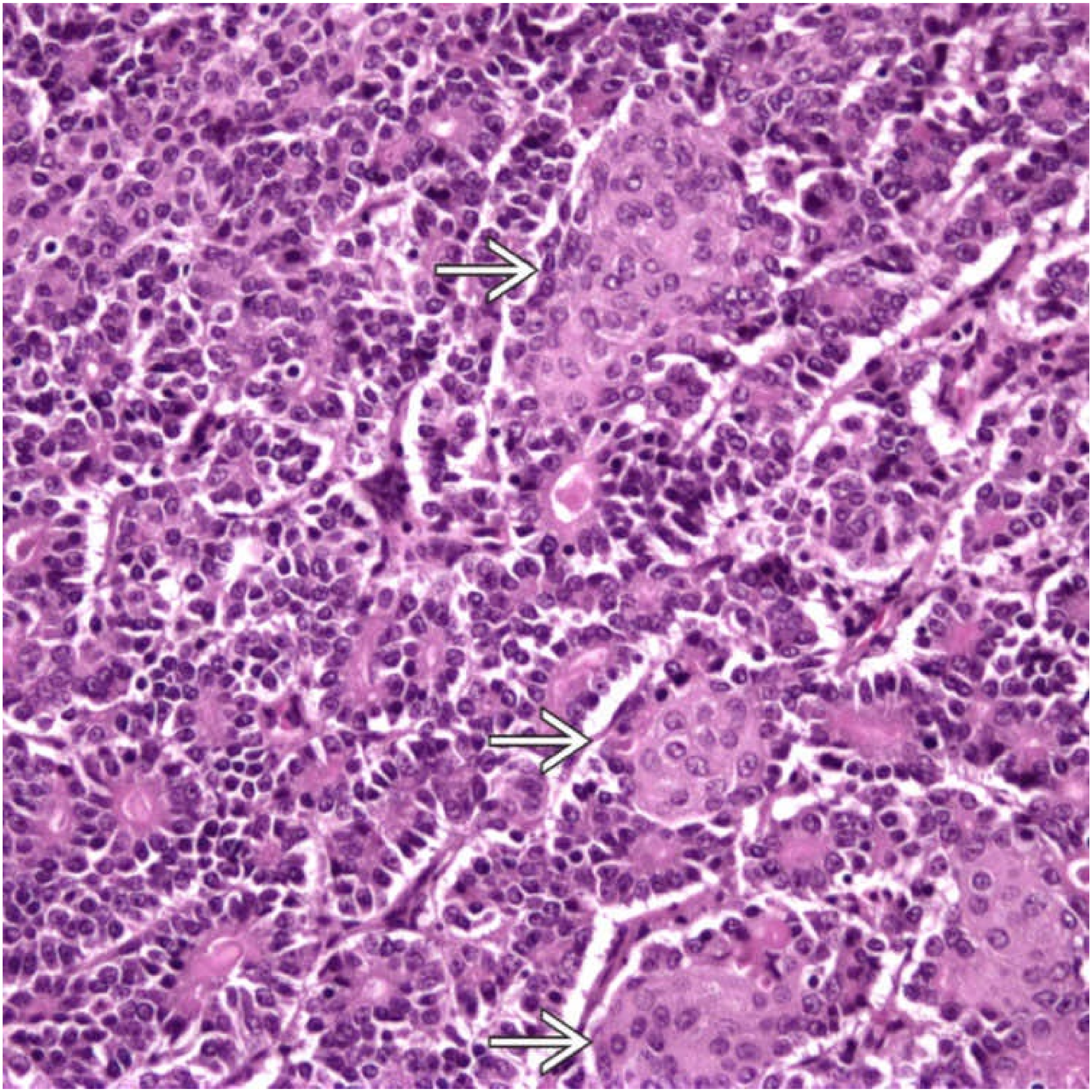
- Lobular growth pattern with distinct fibrous bands
  - Multiple histologic patterns
  - Acinar pattern usually predominant
  - Squamoid nests virtually always present
  - Endocrine component present in 1/2-2/3 of tumors
  - Variable stromal component
  - Minor ductal or primitive component variably present

Top Differential Diagnoses

- Acinar cell carcinoma
- Well-differentiated pancreatic endocrine tumor
- Solid pseudopapillary neoplasm

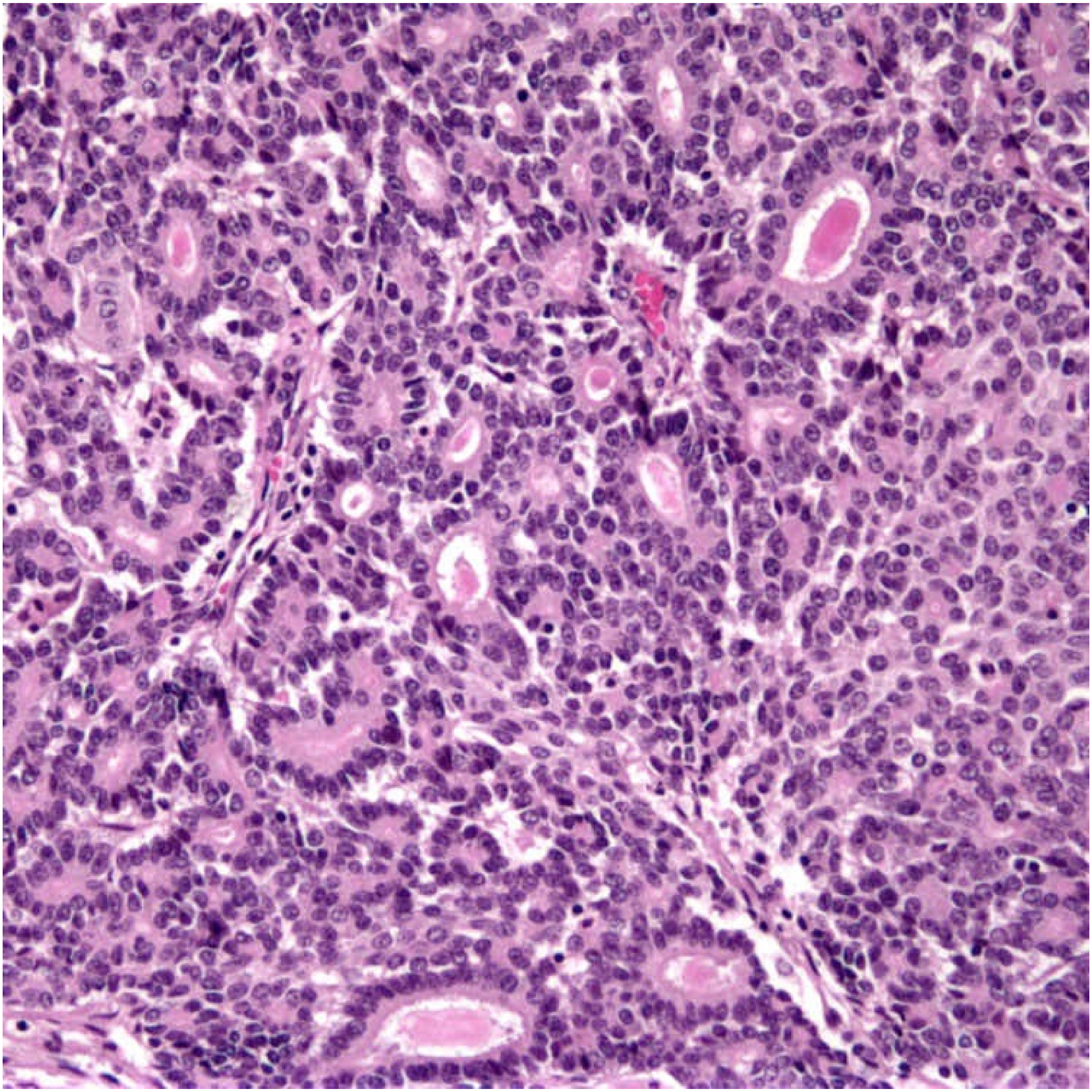


Lobular Growth Pattern
This low-power photomicrograph illustrates the lobular growth pattern of pancreatoblastoma as well as the prominent fibrous stroma.

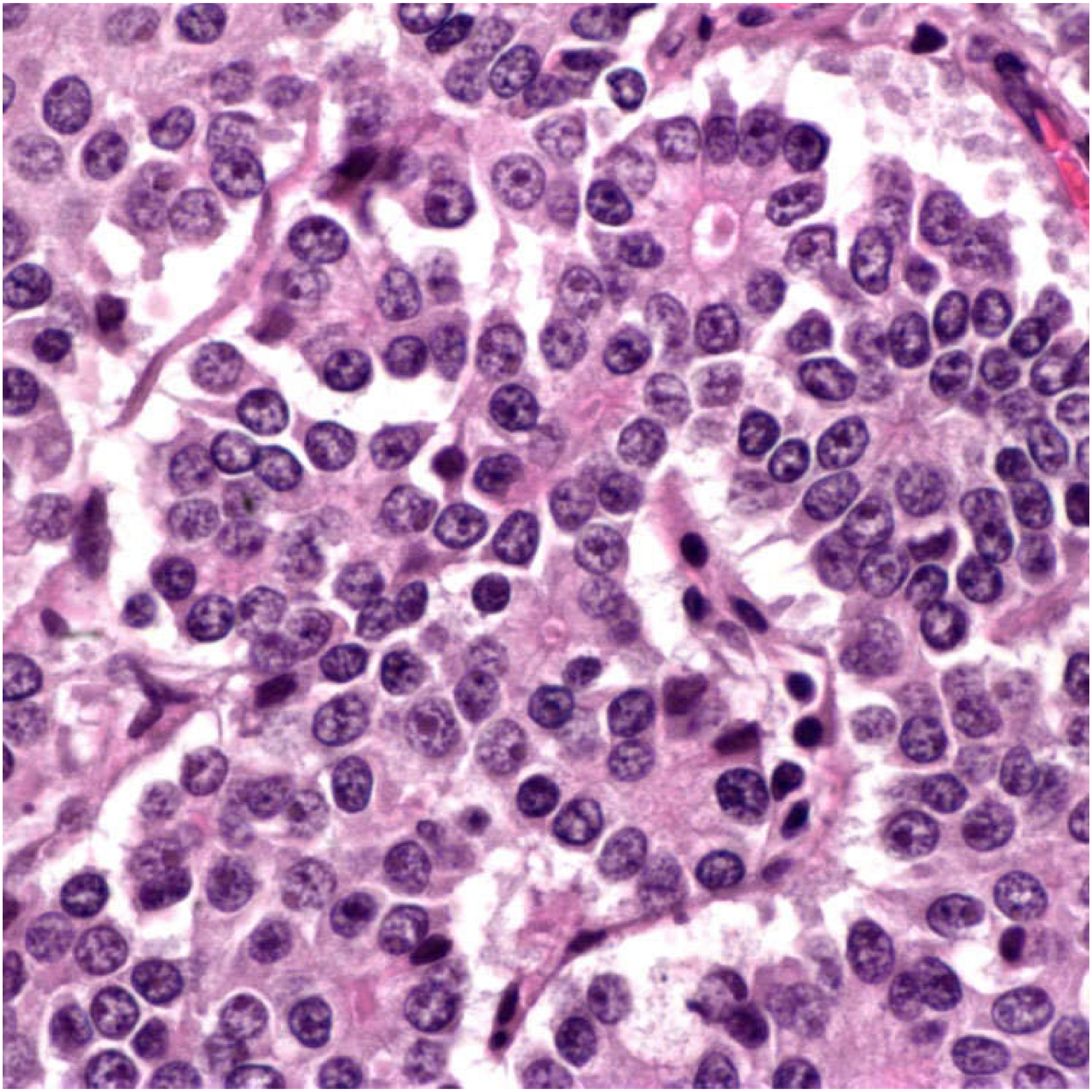


Squamoid Nests

Squamoid nests ⇒ are invariably present in pancreatoblastoma, seen here admixed with areas of acinar differentiation.



Acinar Pattern
The acinar pattern is one of the most common patterns of differentiation in pancreatoblastoma. The uniform cells are arranged around small lumina.



High Magnification of Acinar Pattern
The acinar pattern is characterized by acinar structures with small lumina and basally located uniform nuclei. Prominent nucleoli may be seen, as here.

TERMINOLOGY

Abbreviations

• Pancreatoblastoma (PB)

Definitions

• Malignant epithelial neoplasm with multiple lines of differentiation

- Acinar, squamous, endocrine, ductal, or mesenchymal components may be seen
- Many are associated with mutations in β-catenin/ *APC* pathway
- Minority associated with *SMAD4* (DPC4) alterations

CLINICAL ISSUES

Epidemiology

- Incidence
  - Rare overall but most common malignant pancreatic neoplasm of childhood
  - – 25% of pancreatic tumors in pediatric population
- Age
  - 2/3 occur in children, 1/3 in adults
    - – Bimodal distribution; mean at diagnosis is 2.4 years in children and 40 years in adults
- Sex
  - No sex predominance
- Ethnicity
  - More common in Asians

Presentation

- Upper abdominal mass
  - Large and often palpable in children
- Abdominal pain
- Weight loss
- Jaundice is rare
- May be associated with Beckwith-Wiedemann syndrome (often cystic in this context)

Laboratory Tests

- 25-30% have elevated α-fetoprotein (AFP)

Treatment

- Surgery is treatment of choice
- Chemotherapy and radiation have been used for unresectable disease or recurrence

Prognosis

- Aggressive neoplasm
  - 1/3 have metastases at time of diagnosis
  - – Typically occur in liver, lymph nodes, lungs, peritoneum
- Overall survival only 50%

– Prognosis worse for adults than children

MACROSCOPIC

General Features

- Usually solitary and lobulated
- Equally distributed between head and tail
- Well circumscribed and at least partially encapsulated
- Gray, tan, or yellow cut surface with variably present necrosis

Size

- Large (mean: 10-11 cm)

MICROSCOPIC

Histologic Features

- Lobular growth pattern with distinct fibrous bands
    - Multiple histologic patterns
    - ○ Acinar pattern
    - – Usually predominant
    - – Cells polarized around small lumina
    - – Uniform basal nuclei with single nucleolus

○ Squamoid nests
– Virtually always present, usually in center of tumor lobules
– Whorled, plump, sometimes spindled cells with eosinophilic cytoplasm
– Variably present keratinization
○ Endocrine component
– Present in 1/2-2/3 of tumors
– Endocrine cells either scattered within acini or form trabeculae or nests
○ Stromal component
– Ranges from paucicellular to highly cellular
– May contain foci of cartilage or osseous differentiation
○ Primitive component: Variably present, composed of monotonous immature small blue cells
○ Ductal component: Rare and usually focal

ANCILLARY TESTS

Immunohistochemistry

- Acinar component stains with keratins (7, 8, 18, 19, CAM5.2, AE1/AE3), pancreatic enzymes; may stain with AFP
- Endocrine component stains with synaptophysin, chromogranin, NSE; does not stain with insulin, glucagon, or somatostatin
- Squamoid nests are often not immunoreactive; may have nuclear ß-catenin immunoreactivity

DIFFERENTIAL DIAGNOSIS

Acinar Cell Carcinoma

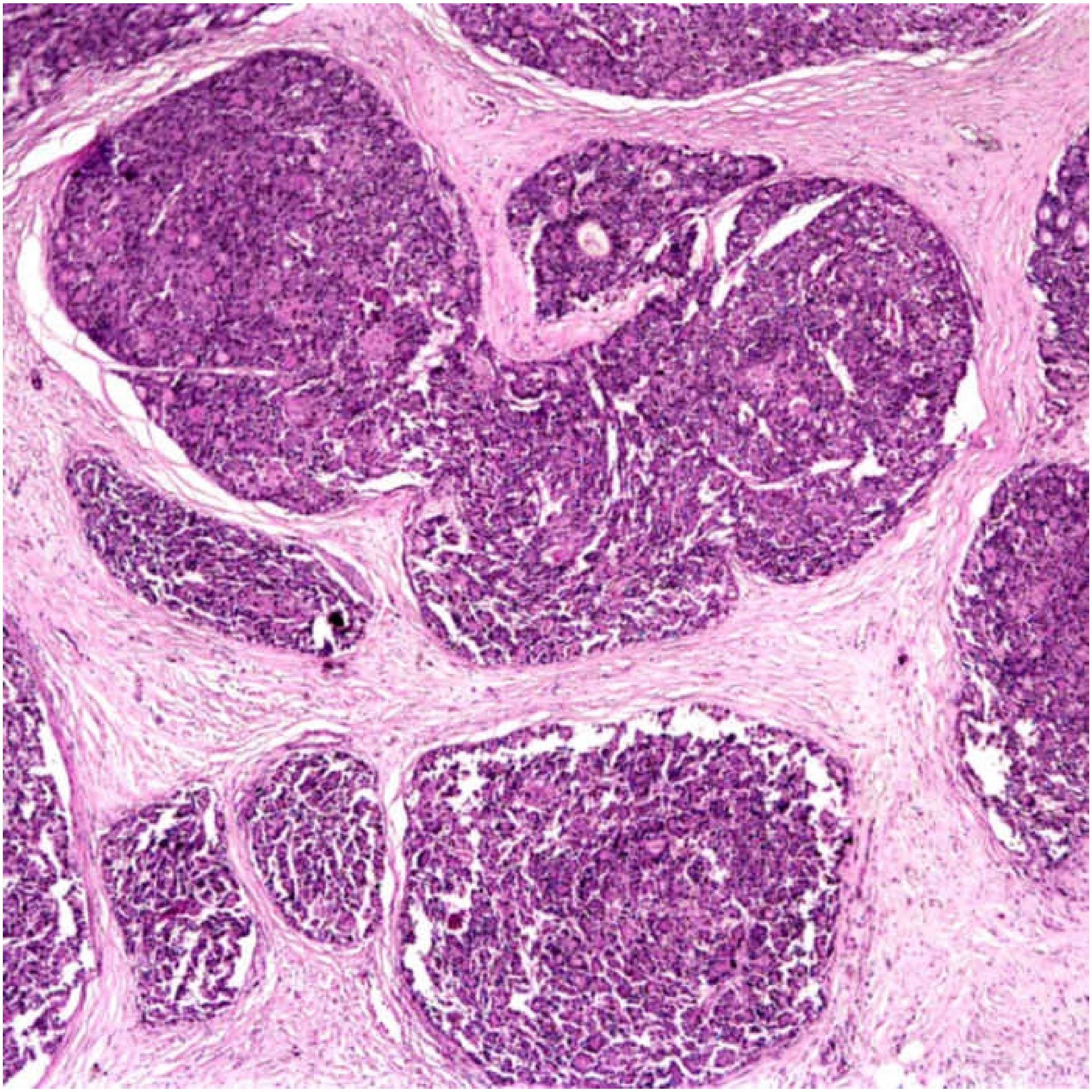
- Lacks squamoid nests and prominent stromal component
- Usually in older patients

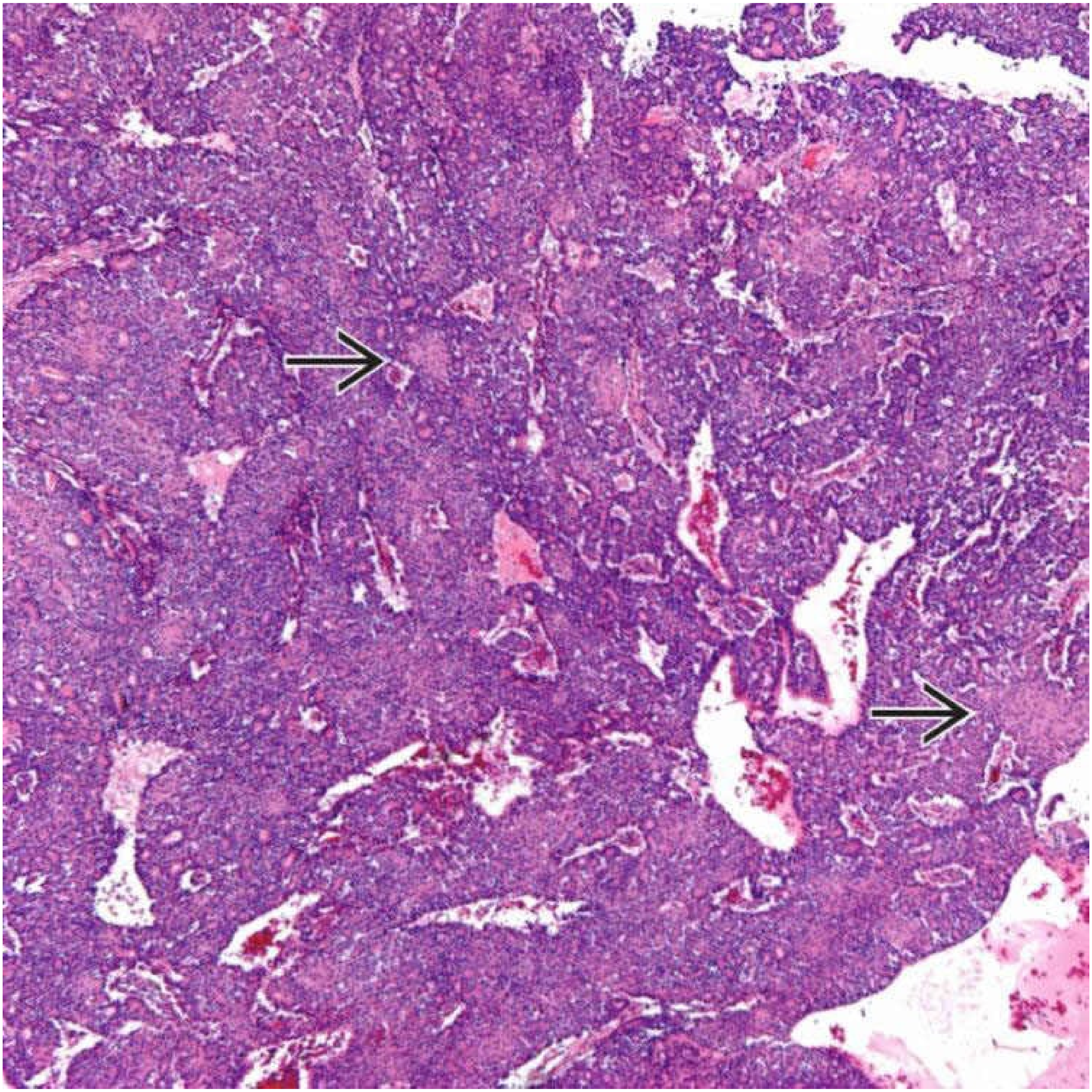
Well-Differentiated Pancreatic Endocrine Tumor

- Uniform endocrine differentiation, negative for acinar markers
- Lacks squamoid nests

Solid-Pseudopapillary Neoplasm

- Pseudopapillary pattern, foamy macrophages, cholesterol clefts; lacks squamoid nests
- Usually in young adult females
- CD10(+); negative for pancreatic enzyme stains


Low-power photomicrograph illustrates the lobular growth pattern of pancreatoblastoma as well as the prominent fibrous stroma.



This pancreatoblastoma has a more solid pattern with less prominent stroma. Note the squamoid nests →, which are visible even at low power.

SELECTED REFERENCES

1. Hackeng, WM, et al. Surgical and molecular pathology of pancreatic neoplasms. *Diagn Pathol*. 2016; 11(1):47.
2. Omiyale, AO. Clinicopathological review of pancreatoblastoma in adults. *Gland Surg*. 2015; 4(4):322–328.
3. Wood, LD, et al. Pathology and genetics of pancreatic neoplasms with acinar differentiation. *Semin Diagn Pathol*. 2014. [ePub].

4. Muguerza, R, et al. Pancreatoblastoma associated with incomplete Beckwith-Wiedemann syndrome: case report and review of the literature. *J Pediatr Surg*. 2005; 40(8):1341–1344.
5. Hua, C, et al. Pancreatoblastoma: a histochemical and immunohistochemical analysis. *J Clin Pathol*. 1996; 49(11):952–954.
6. Levey, JM, et al. Adult pancreatoblastoma: a case report and review of the literature. *Am J Gastroenterol*. 1996; 91(9):1841–1844.
7. Klimstra, DS, et al. Pancreatoblastoma. A clinicopathologic study and review of the literature. *Am J Surg Pathol*. 1995; 19(12):1371–1389.

Dermoid Cyst

KEY FACTS

Terminology

- Squamous-lined cyst with differentiation along multiple germlines
  - Those reported in pancreas have had only ectodermal elements

Clinical Issues

- Extremely rare
  - Only handful of cases reported
- Patients present with nonspecific gastrointestinal symptoms
  - Presence of palpable mass is common
- No known malignant potential

Macroscopic

- Unilocular tumor, often variegated solid and cystic
- Involves head, body, or tail of pancreas
- Does not communicate with main pancreatic duct

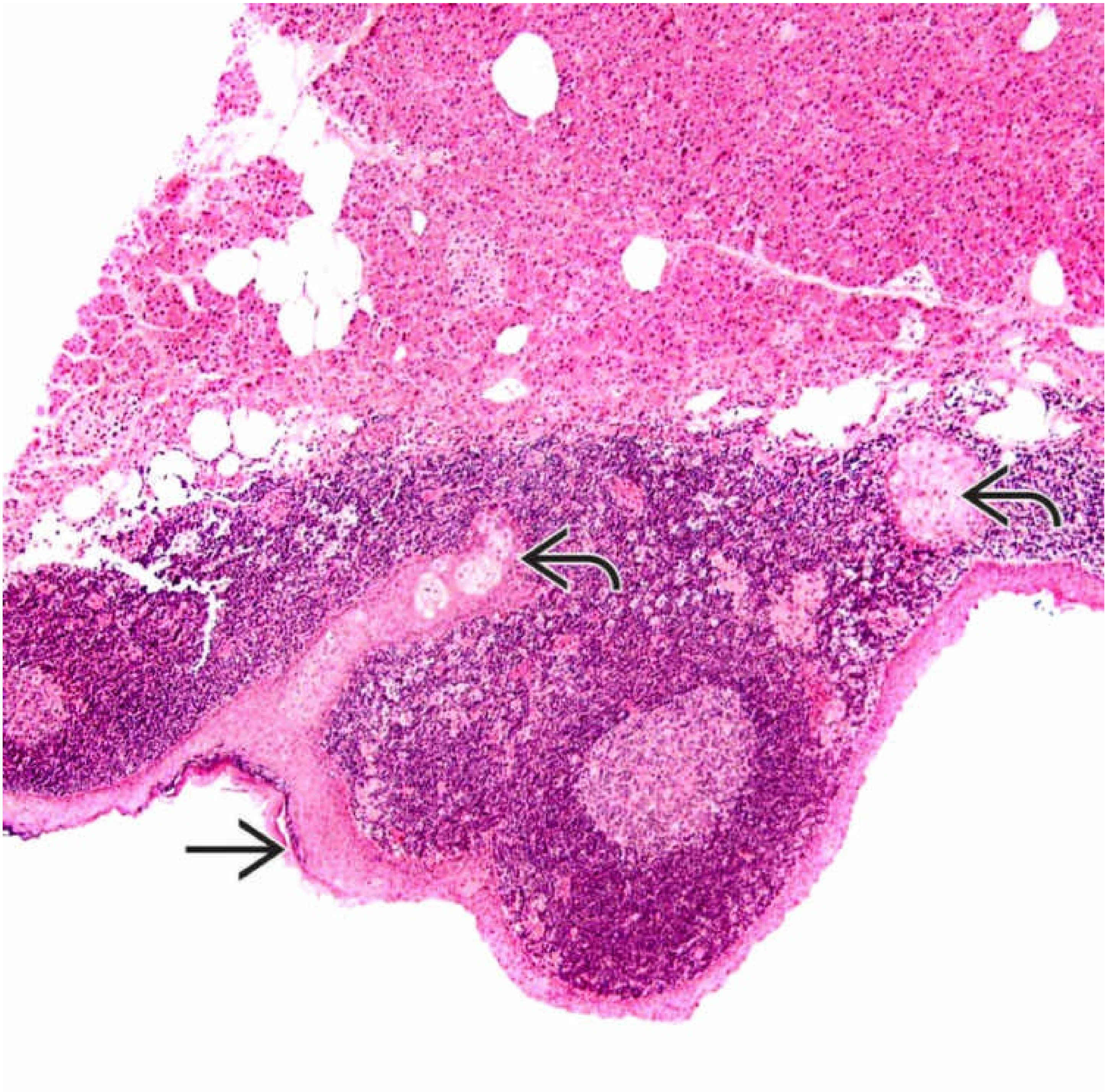
Microscopic

- Similar to dermoid cysts of other organs
  - Multilayered mature squamous epithelium without atypia
  - Adnexal structures present, such as sebaceous glands and hair follicles
  - Mesodermal tissue, such as cartilage, is only rarely present in pancreas
- Mesodermal tissue, such as cartilage, is only rarely present

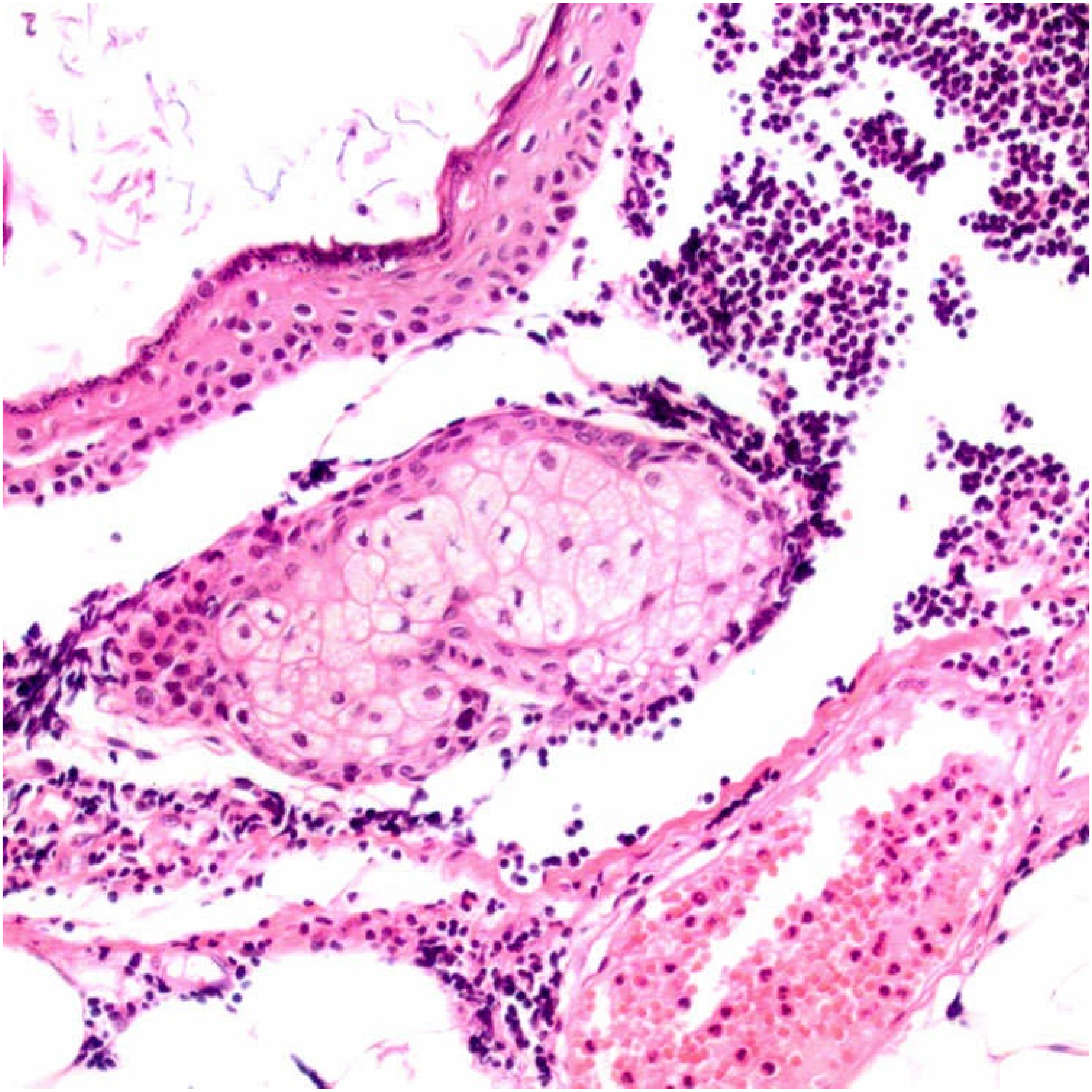
Top Differential Diagnoses

- Lymphoepithelial cyst
  - Significant overlap between lymphoepithelial cyst and dermoid cyst

• Epidermoid cyst in intrapancreatic splenic tissue
• Pancreatic squamous cyst
• Retention cyst

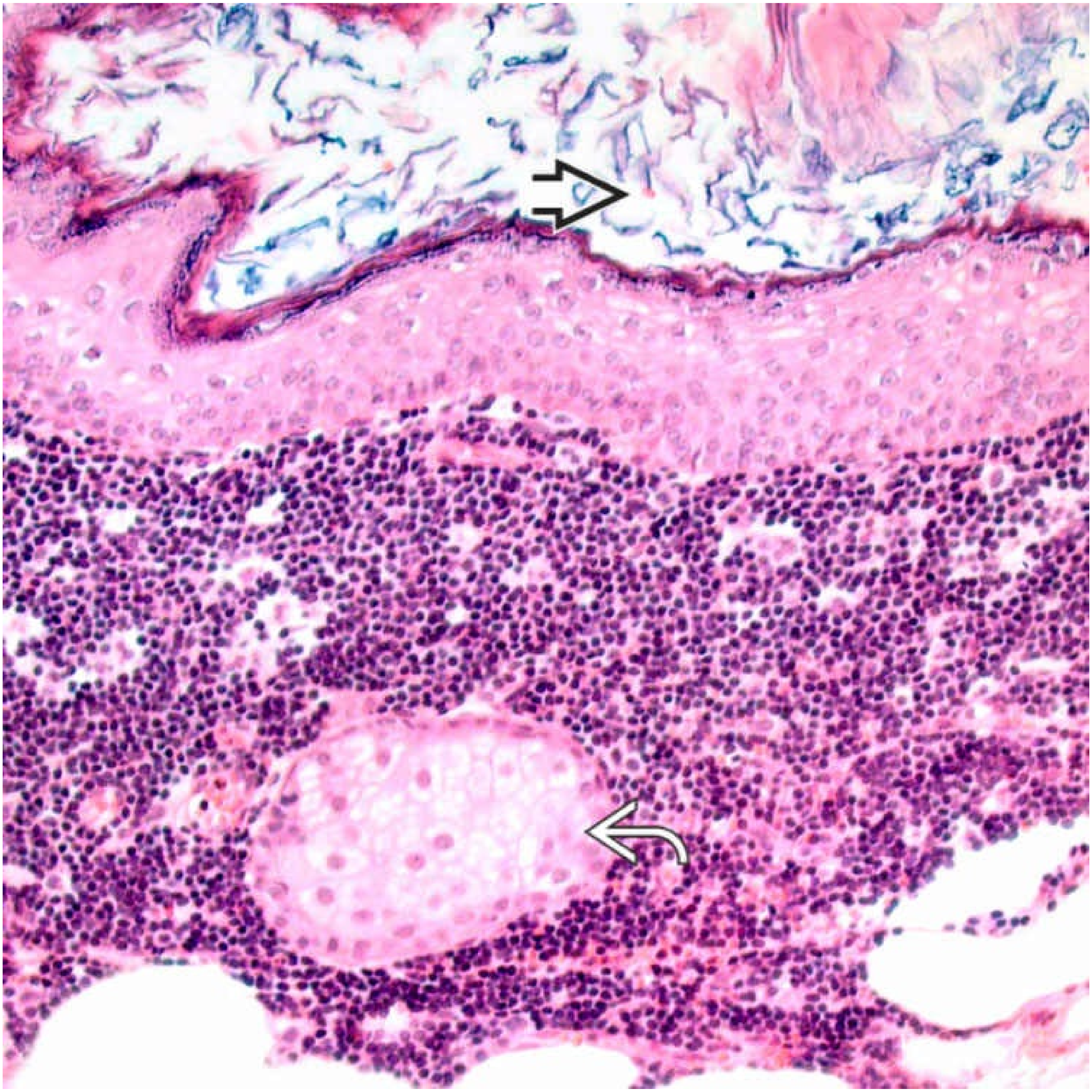


Squamous Lining With Lymphoid Tissue
This pancreatic dermoid cyst is lined by squamous epithelium → with underlying prominent lymphoid tissue. There is extensive sebaceous differentiation ↱ .



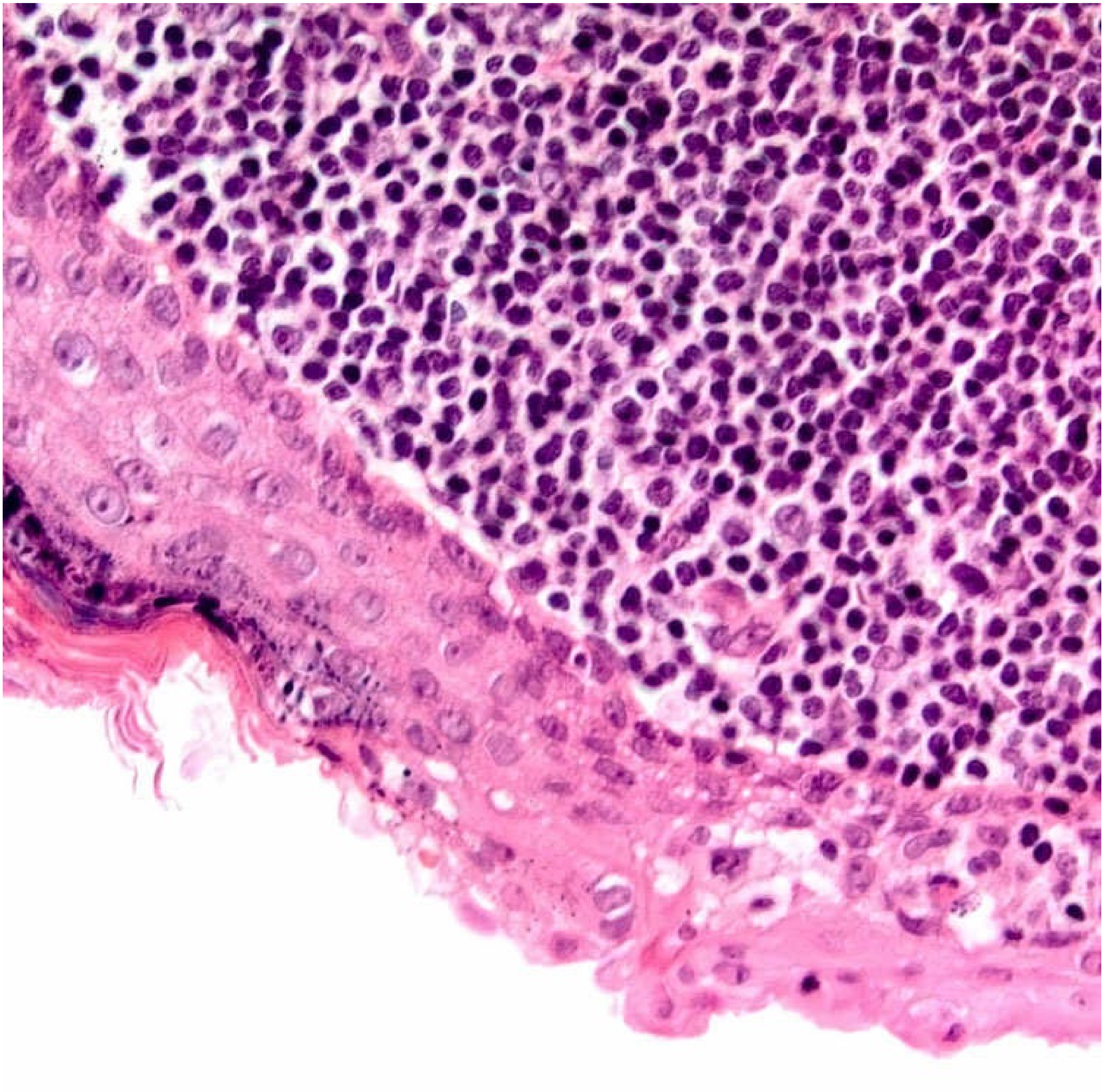
Cyst Wall: Low Power

This dermoid cyst contains mature squamous epithelium with underlying sebaceous glands and lymphoid tissue. Mesodermal differentiation is only rarely present in dermoid cysts of the pancreas.



Sebaceous Differentiation

The squamous lining epithelium is mature and shows surface keratinization. Sebaceous differentiation is evident in the wall .



Mature Keratinizing Epithelium
This high-power view from a section of a dermoid cyst shows mature keratinizing squamous epithelium with underlying lymphoid stroma.

TERMINOLOGY

Synonyms

- Mature cystic teratoma
- Monodermal teratoma

Definitions

- Squamous-lined cyst with differentiation along multiple germlines
  - Those reported in pancreas have had only ectodermal elements

CLINICAL ISSUES

Epidemiology

- Incidence
  - Extremely rare
  - Only handful of cases reported
- Age
  - Range: 2-53 years
    - Mean: 29 years

Presentation

- Nonspecific gastrointestinal symptoms
  - Nausea and vomiting
  - Malaise
  - Epigastric pain
  - Weight loss
  - Dyspepsia
- Palpable mass

Treatment

- Surgical approaches
  - May include pancreaticoduodenectomy, distal pancreatectomy, or enucleation
  - Nonoperative management is feasible in cases with firm preoperative diagnosis

Prognosis

- No known malignant potential

IMAGING

General Features

- Variegated solid/cystic mass, variably present calcification

MACROSCOPIC

General Features

- Unilocular tumor

- Often variegated solid and cystic
- Contents appear pasty or cheesy
- Involves head, body, or tail of pancreas
- Dermoid cysts typically do not communicate with pancreatic ductal system

MICROSCOPIC

Histologic Features

- Similar to dermoid cysts of other organs
  - Multilayered mature squamous epithelium without atypia
  - Adnexal structures present, such as sebaceous glands and hair follicles
  - Other cell types (e.g., respiratory epithelium) have been reported
- Pancreatic dermoid cysts are predominantly monodermal
  - Mesodermal tissue, such as cartilage, is only rarely present

Cytologic Features

- Anucleated squamous cells
- Necrotic debris
- May have prominent lymphoid component

DIFFERENTIAL DIAGNOSIS

Lymphoepithelial Cyst

- Lined by squamous epithelium with prominent layer of lymphoid tissue
  - Occasionally, sebaceous glands may be found, but other adnexal structures are absent
  - Nonetheless, there exists overlap between lymphoepithelial cysts and dermoid cysts
  - Extensive sebaceous differentiation may indicate dermoid cyst

Epidermoid Cyst in Intrapancreatic Splenic Tissue

- Splenic pulp is present

Pancreatic Squamous Cyst

- Lined by squamous epithelium but lacks adnexal structures

Serous Cystadenoma

- Lined by single, occasionally multilayered, epithelium with clear cytoplasm
- Lacks adnexal structures, lymphoid tissue, and mesodermal elements

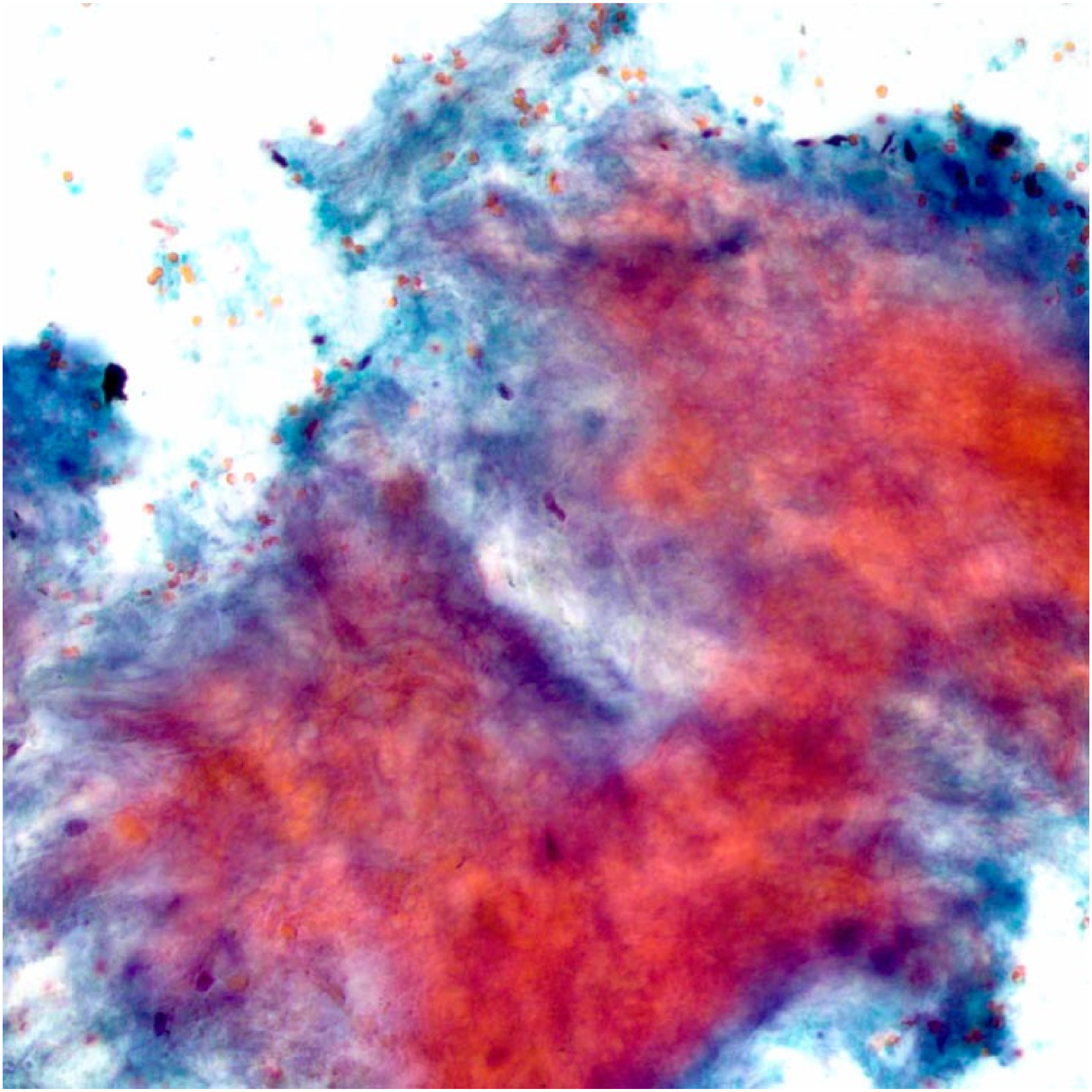
Mucinous Cystic Neoplasm and Intraductal Papillary

Mucinous Neoplasm

- Mucin-producing cells dominate epithelium lining
- Lacks squamous, adnexal, and lymphoid components
- Intraductal papillary mucinous neoplasm communicates with pancreatic duct

Retention Cyst

- Lined by simple cuboidal epithelium
- When present, squamous differentiation is focal
- Lacks lymphoid stroma, adnexal structures



This pancreatic cyst aspirate cyst shows anucleate squamous cells, which could be seen either in a dermoid cyst or a lymphoepithelial cyst.

SELECTED REFERENCES

1. Othman, M, et al. Squamoid cyst of pancreatic ducts: a distinct type of cystic lesion in the pancreas. *Am J Surg Pathol*. 2007; 31(2):291–297.
2. Tucci, G, et al. Dermoid cyst of the pancreas: presentation and management. *World J Surg Oncol*. 2007; 5:85.
3. Adsay, NV, et al. Lymphoepithelial cysts of the pancreas: a report of 12 cases and a review of the literature. *Mod Pathol*. 2002; 15(5):492–501.
4. Adsay, NV, et al. Squamous-lined cysts of the pancreas: lymphoepithelial cysts, dermoid cysts (teratomas), and accessory-splenic epidermoid cysts. *Semin Diagn Pathol*. 2000; 17(1):56–65.

5. Mandavilli, SR, et al. Lymphoepithelial cyst (LEC) of the pancreas: cytomorphology and differential diagnosis on fine-needle aspiration (FNA). *Diagn Cytopathol*. 1999; 20(6):371–374.

Poorly Differentiated Neuroendocrine Carcinoma, Pancreas

KEY FACTS

Terminology

- Morphological and immunohistochemical features suggestive of neuroendocrine differentiation
  - High proliferation
  - Mitoses > 20 in 10 HPF (based on count of at least 50 HPF; 1 HPF = 2 mm^2), or
  - Ki-67 labeling index > 20% based on at least 500 tumor cells (2,000 if possible)

Clinical Issues

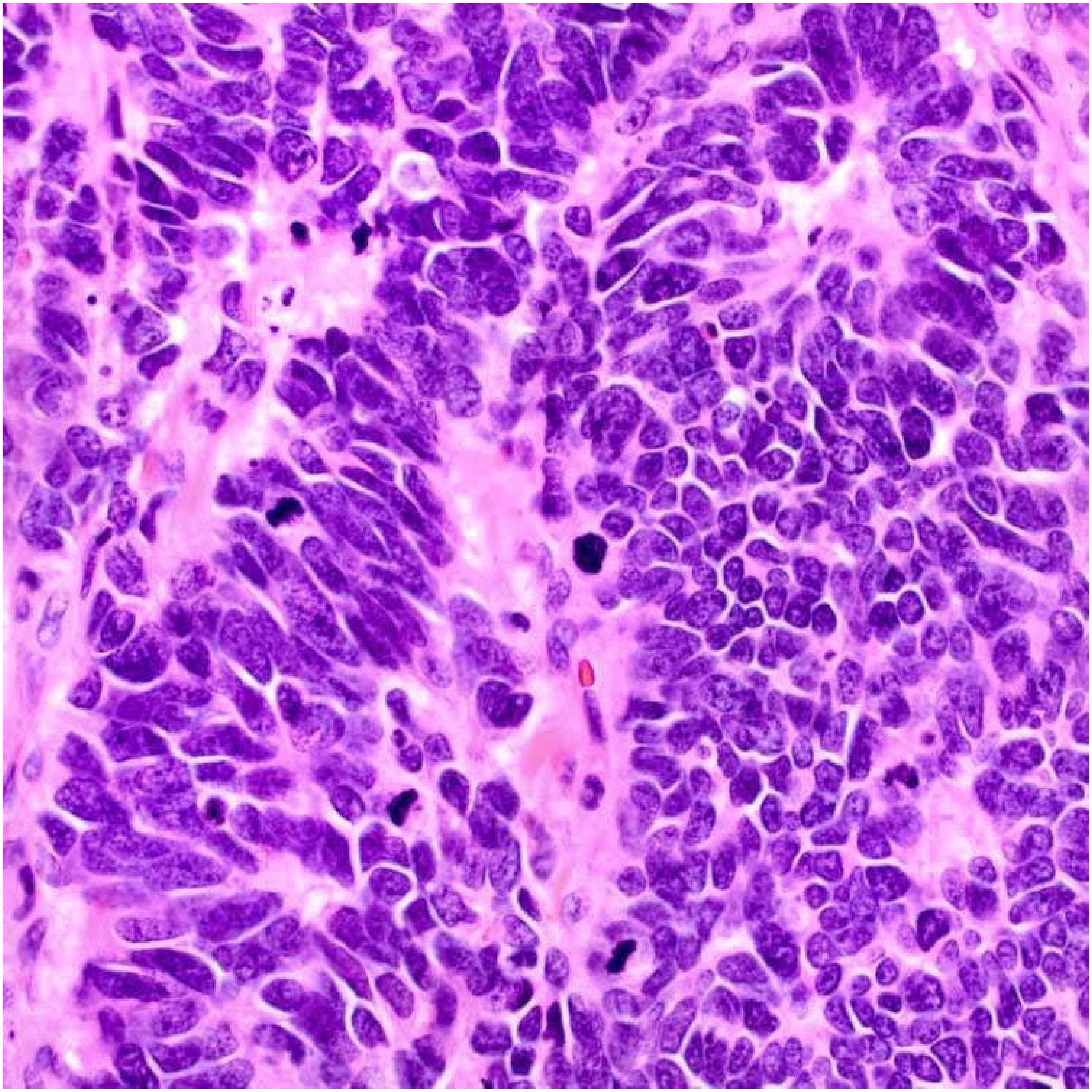
- Very aggressive neoplasms
- Platinum-based chemotherapy (cisplatin or carboplatin) with etoposide
- Large cell morphology, positivity for both synaptophysin and chromogranin, and Ki-67 index < 55% have been reported as favorable parameters

Microscopic

- Small cell variant
  - Resembles small cell carcinomas of lung
  - Scant cytoplasm, hyperchromatic nuclei, prominent nuclear moulding
- Large cell variant
  - Resembles large cell neuroendocrine carcinoma of lung

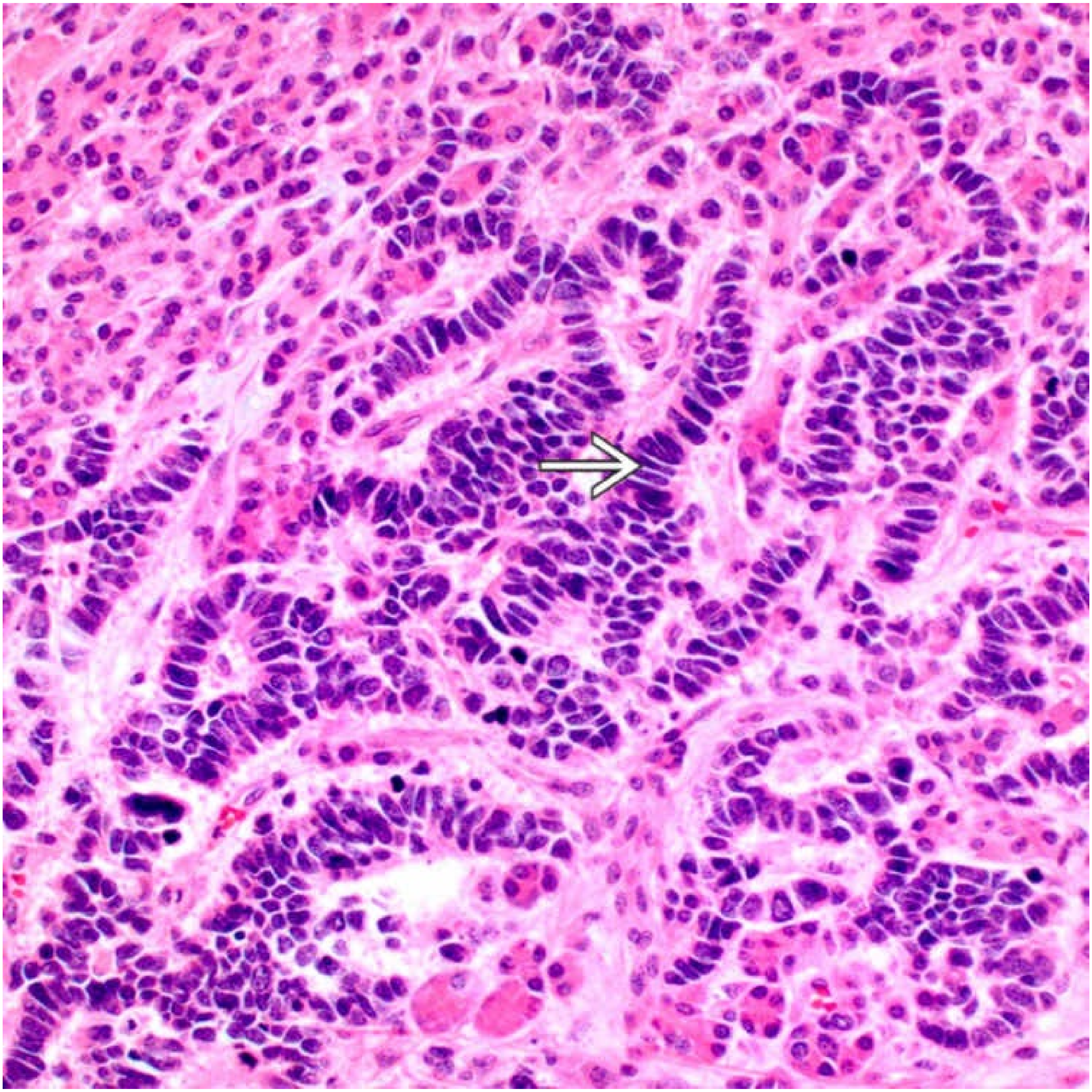
Ancillary Tests

- Neuroendocrine markers, keratin (+)
- Ki-67 proliferation index: Often necessary to determine grade and guide choice of therapy
- Mitoses and Ki-67 index should be counted in areas with highest proliferation ("hot spots")

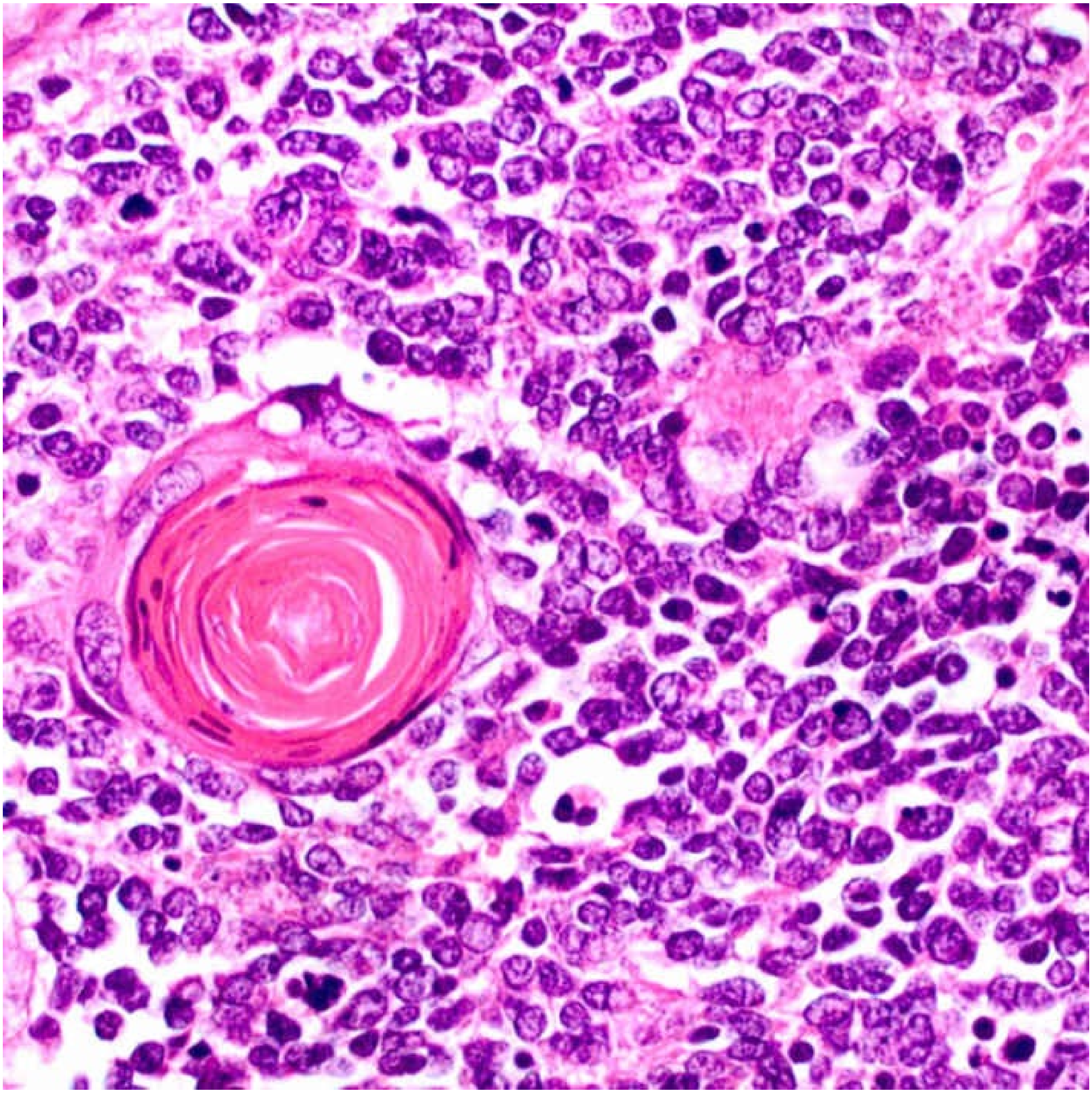


Small Cell Neuroendocrine Carcinoma

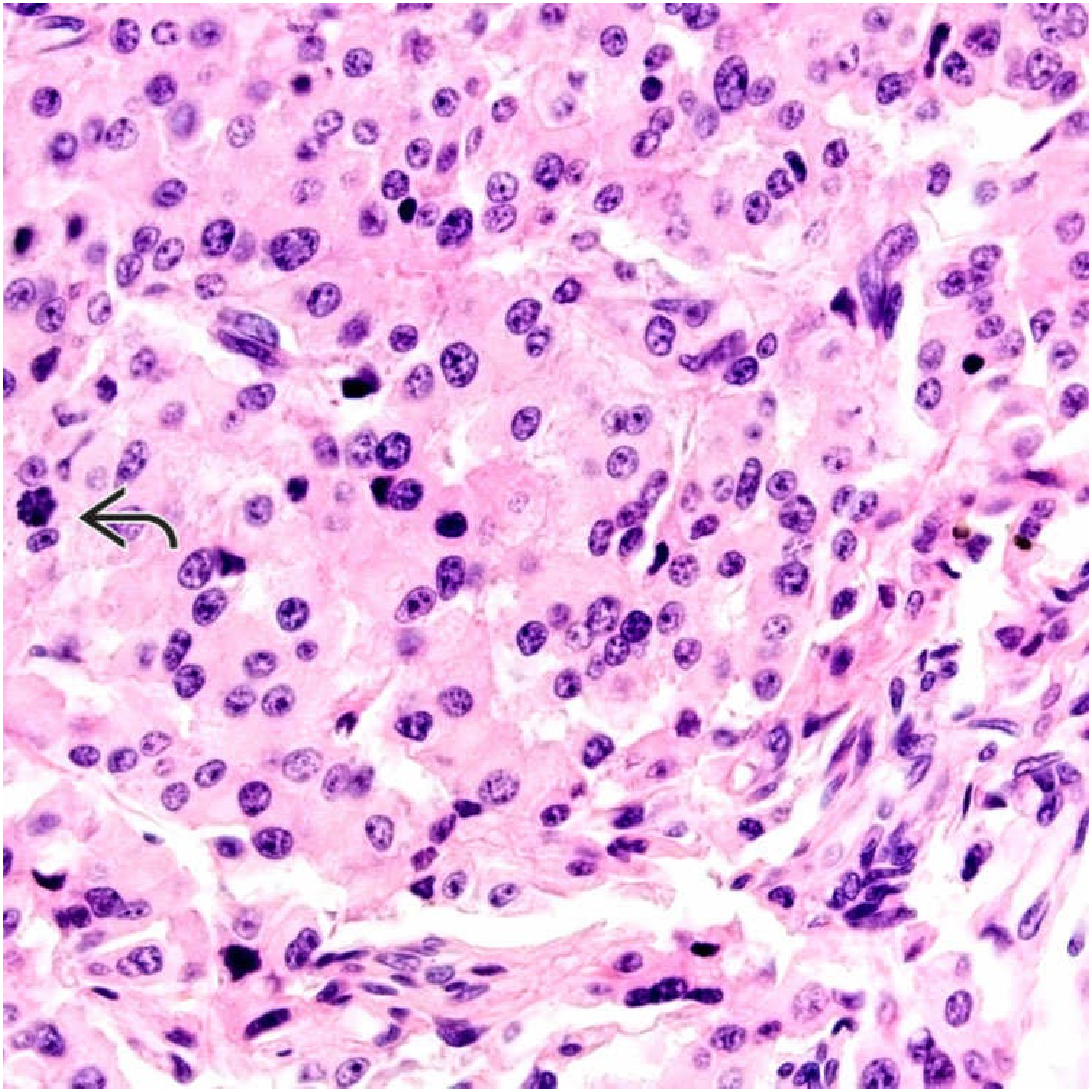
Small to medium-sized tumor cells with scant cytoplasm, indistinct nucleoli, molding, brisk mitoses and karyorrhectic debris are present.



Metastatic Small Cell Neuroendocrine Carcinoma
Pancreatic primary tumor metastatic to liver shows typical cytologic features of small cell neuroendocrine carcinoma, including prominent nuclear molding ⇒. Absence of significant cytoplasm or prominent nucleoli distinguishes it from large cell neuroendocrine carcinoma.



Focal Squamous Differentiation
Squamous cells with keratin pearls indicating focal squamous differentiation in an otherwise typical small cell neuroendocrine carcinoma are shown.



Large Cell Neuroendocrine Carcinoma
The presence of abundant cytoplasm, prominent nucleoli, and brisk mitoses (30 mitoses/10 HPF) are typical features of large cell neuroendocrine carcinoma.

TERMINOLOGY

Synonyms

- High-grade neuroendocrine carcinoma
- Poorly differentiated neuroendocrine carcinoma

Definitions

- Morphological and immunohistochemical features suggestive of neuroendocrine differentiation
  - High proliferation
    - Mitoses > 20 in 10 HPF (based on count of at least 50 HPF), or
    - Ki-67 labeling index > 20% based on at least 500 tumor cells

ETIOLOGY/PATHOGENESIS

Unknown

- Do not arise from low-grade neuroendocrine tumors in most cases
  - Genetic changes in small and large cell neuroendocrine carcinoma are similar, both are distinct from well-differentiated neuroendocrine tumor
    - Immunohistochemical abnormalities in p53 (> 90%) and Rb (> 70%) common in small cell and large cell neuroendocrine carcinomas
    - Genes typically involved in well-differentiated neuroendocrine tumor like *SMAD4* (DPC4), *DAXX*, and *ATRX* are normal
    - Bcl-2 overexpression common in neuroendocrine carcinomas, especially small cell

CLINICAL ISSUES

Epidemiology

- Incidence
    - Rare, constituting 2-3% of all pancreatic neuroendocrine neoplasms

Presentation

- Jaundice
  - Back pain
  - Some patients present with hormonal symptoms
    - Cushing syndrome
    - Hypercalcemia

Treatment

- Surgical approaches
    - Radical pancreatic surgery
    - Many patients unresectable at diagnosis
- Drugs
    - Platinum-based chemotherapy (cisplatin or carboplatin) with etoposide
    - Alkylating agent temozolomide-based regimen often used as 2nd-line therapy

Prognosis

- Aggressive neoplasms
    - Survival typically few months, less than ductal adenocarcinoma of pancreas

- Favorable parameters
  - Large cell morphology
  - Positivity for both synaptophysin and chromogranin on immunohistochemistry
  - Ki-67 index < 55%

MACROSCOPIC

Size

- Typically large tumors
  - Solid white to tan

MICROSCOPIC

Histologic Features

- Small cell variant
  - Resembles small cell carcinoma of lung
  - Diffuse sheet-like arrangement of cells
  - – Cytologic features
  - ☐ Small to medium-sized cells
  - ☐ Scant cytoplasm
  - ☐ Hyperchromatic nuclei, gritty chromatin
  - ☐ Prominent nuclear molding
  - ☐ Inconspicuous nucleoli
- Necrosis invariably seen; varies from punctate foci to geographic necrosis
- Extensive vascular and perineural invasion is common
- Mitotic figures typically > 50/10 HPF

– By definition, at least 20 mitotic figures/10 HPF are required if grading is being done based on mitoses alone

– Mitoses should be counted in areas with highest proliferation (“hot spots”)

- Large cell variant
  - Resembles large cell neuroendocrine carcinoma of lung
  - Neuroendocrine architecture: Nests and trabeculae
    - Cytologic features
      - ☐ Medium to large-sized cells
      - ☐ Moderate to abundant eosinophilic cytoplasm
      - ☐ Vesicular nuclei
      - ☐ Prominent nucleoli
    - Gland formation is not typical feature
  - Vascular invasion and necrosis often present

ANCILLARY TESTS

Immunohistochemistry

- Chromogranin and synaptophysin
  - Positive but reactivity may be focal &/or weak
  - Not required for diagnosis of small cell neuroendocrine carcinoma
  - Positivity for at least 1 marker required for diagnosis of large cell neuroendocrine carcinoma
- Cytokeratin (+)
- Ki-67 proliferation index
  - "Eyeballing" should not be used except for cases with very low or very high proliferative index
  - Best determined by counting in static images in "hot spot" areas
  - Counting of overlapping cells and lymphocytes are pitfalls with automated image analysis systems
  - Free Internet resource is available (ImmunoRatio) but needs to be used with caution
  - Heterogeneity in tumor may lead to undergrading in biopsies
  - If discrepancy between mitotic count and Ki-67 index, higher grade should be used

DIFFERENTIAL DIAGNOSIS

Neuroendocrine Tumor, Low Grade

- Mitoses < 20 per 10 HPF
- Lack nuclear features of small cell or large cell neuroendocrine carcinoma

Poorly Differentiated Adenocarcinoma

- Lacks histologic and immunohistochemical evidence of neuroendocrine differentiation
- Gland formation usually present

Metastatic Small Cell Carcinomas From Lung

- TTF-1(+)
  - Extrapulmonary small cell carcinomas can be TTF-1(+)

Other Malignant Round Cell Tumors

- Rhabdomyosarcoma: Desmin and myogenin (+)
- Desmoplastic round cell tumor: Cytokeratin, desmin (+)
- Primitive neuroectodermal tumor: CD99(+)

Neuroendocrine Neoplasm With High Proliferative Index

- Not definite entity in WHO 2010 classification
- Recommended term for neuroendocrine neoplasms with mitoses > 20/10 HPF &/or Ki-67 > 20% but low-grade morphology
- Outcome intermediate between low-grade NET and typical NEC

- Role of platinum-based therapy in these tumors is not established
- Likely that these tumors will be formally placed in separate category in next grading scheme

Acinar Cell Carcinoma

- Morphology can resemble large cell neuroendocrine carcinoma
- Immunohistochemistry for trypsin confirms diagnosis
- Neuroendocrine markers (-) or show patchy staining

Mixed Adenoneuroendocrine Carcinoma

- Adenocarcinoma component: Gland formation ± mucin
- Neuroendocrine carcinoma component: Small cell or large cell morphology, positivity for synaptophysin &/or chromogranin
- Each component constitutes at least 30% of tumor (arbitrary criterion used in WHO 2010 scheme)

Poorly Differentiated Squamous Cell Carcinoma

- Lacks histologic and immunohistochemical evidence of neuroendocrine differentiation
- Positive staining for p63 &/or p40

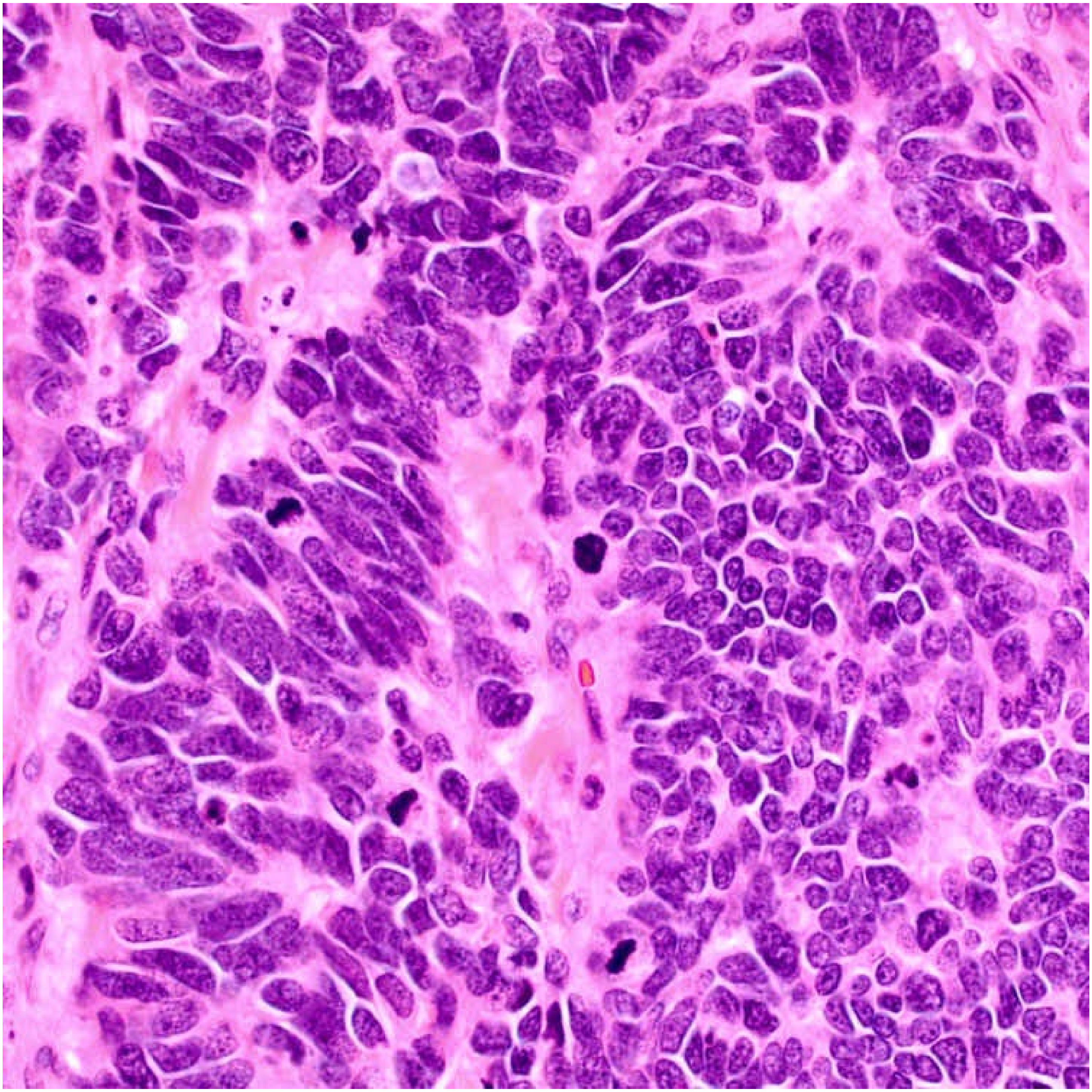
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

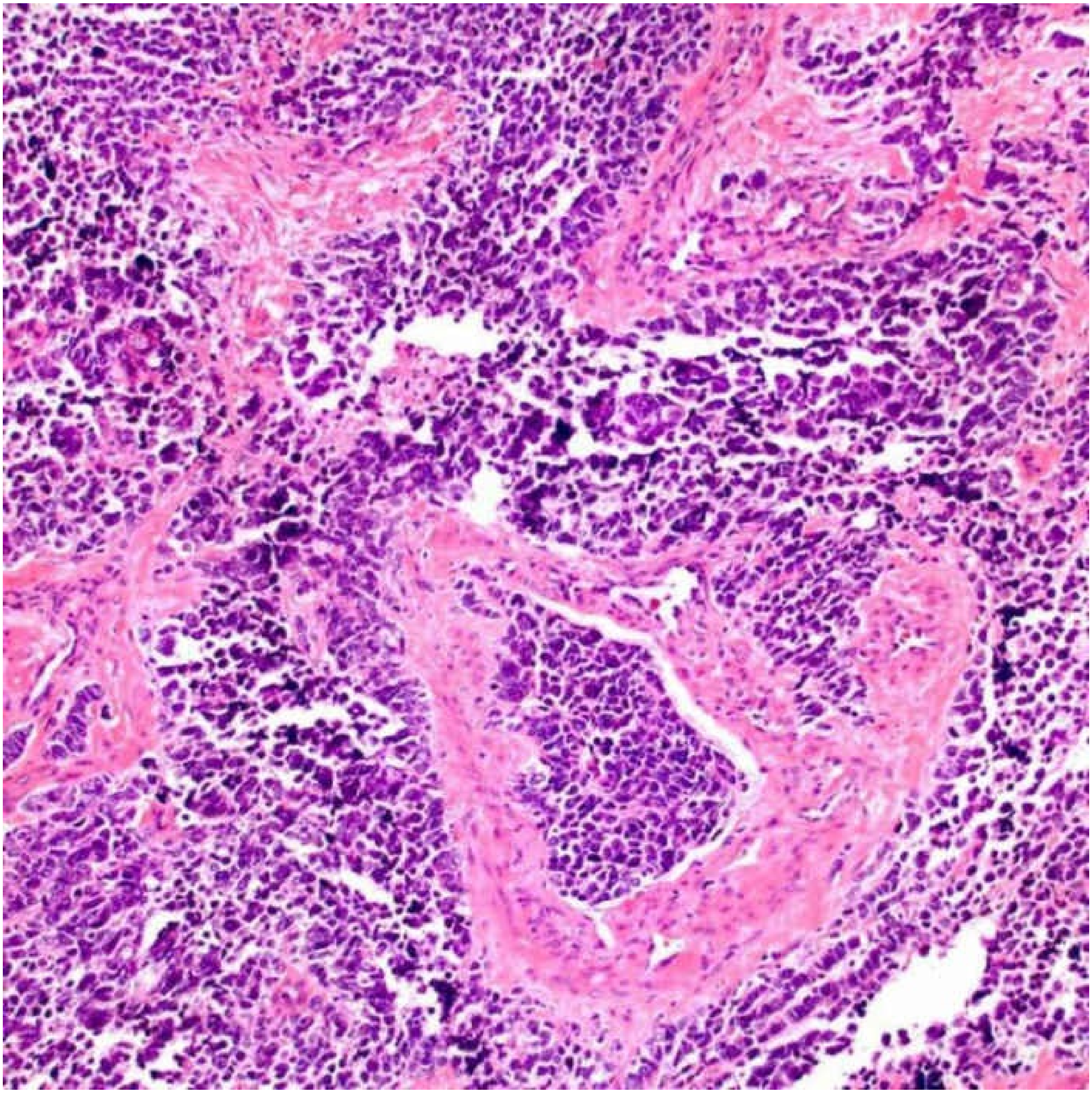
- Important to make diagnosis as patients may benefit from platinum-based chemotherapy

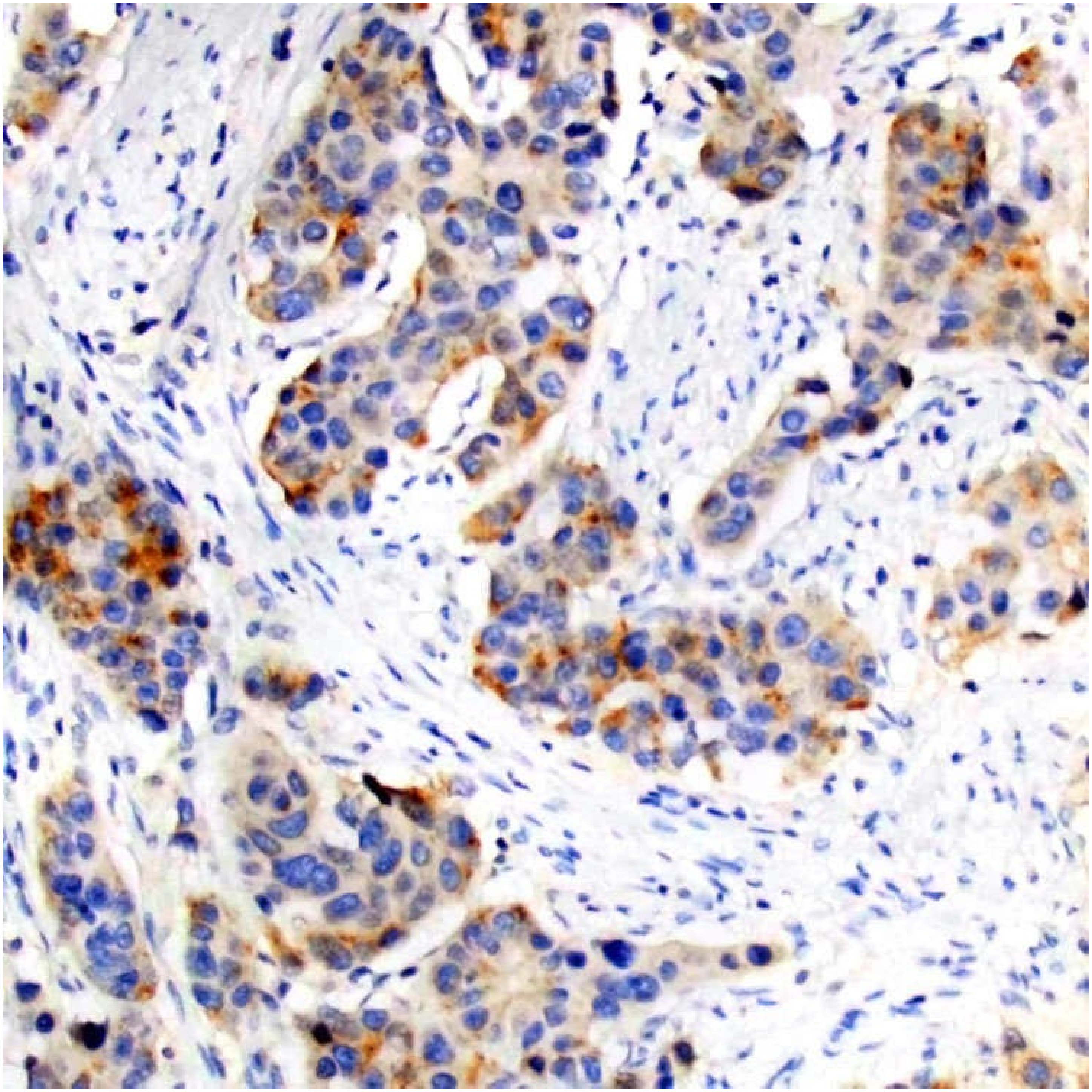
Pathologic Interpretation Pearls

- Tumors resemble their pulmonary counterparts

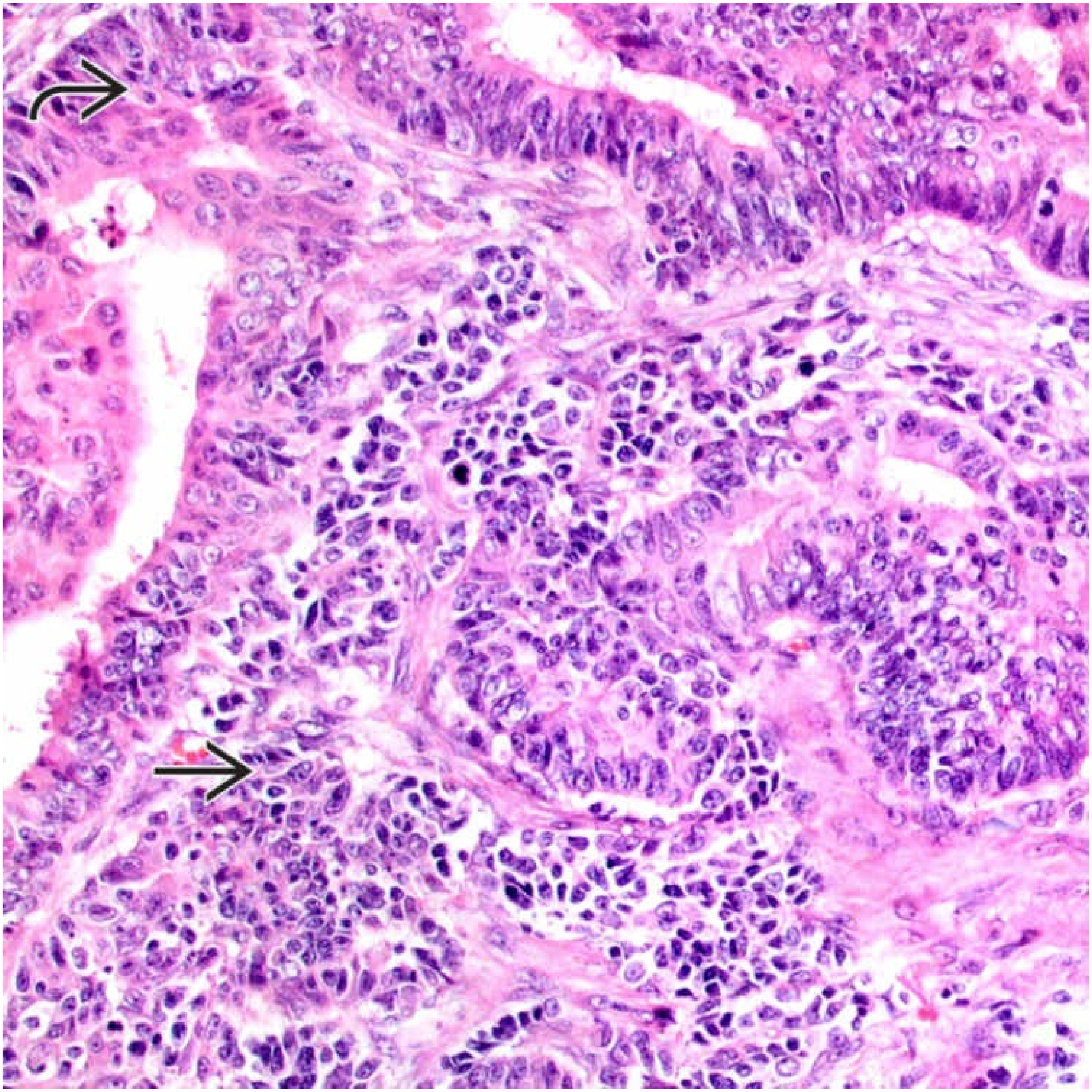


Pancreatic Small Cell Neuroendocrine Carcinoma
Most small cell neuroendocrine carcinomas of the pancreas are virtually identical to small cell carcinoma of the lung. Note the hyperchromatic nuclei with moulding and prominent apoptosis.

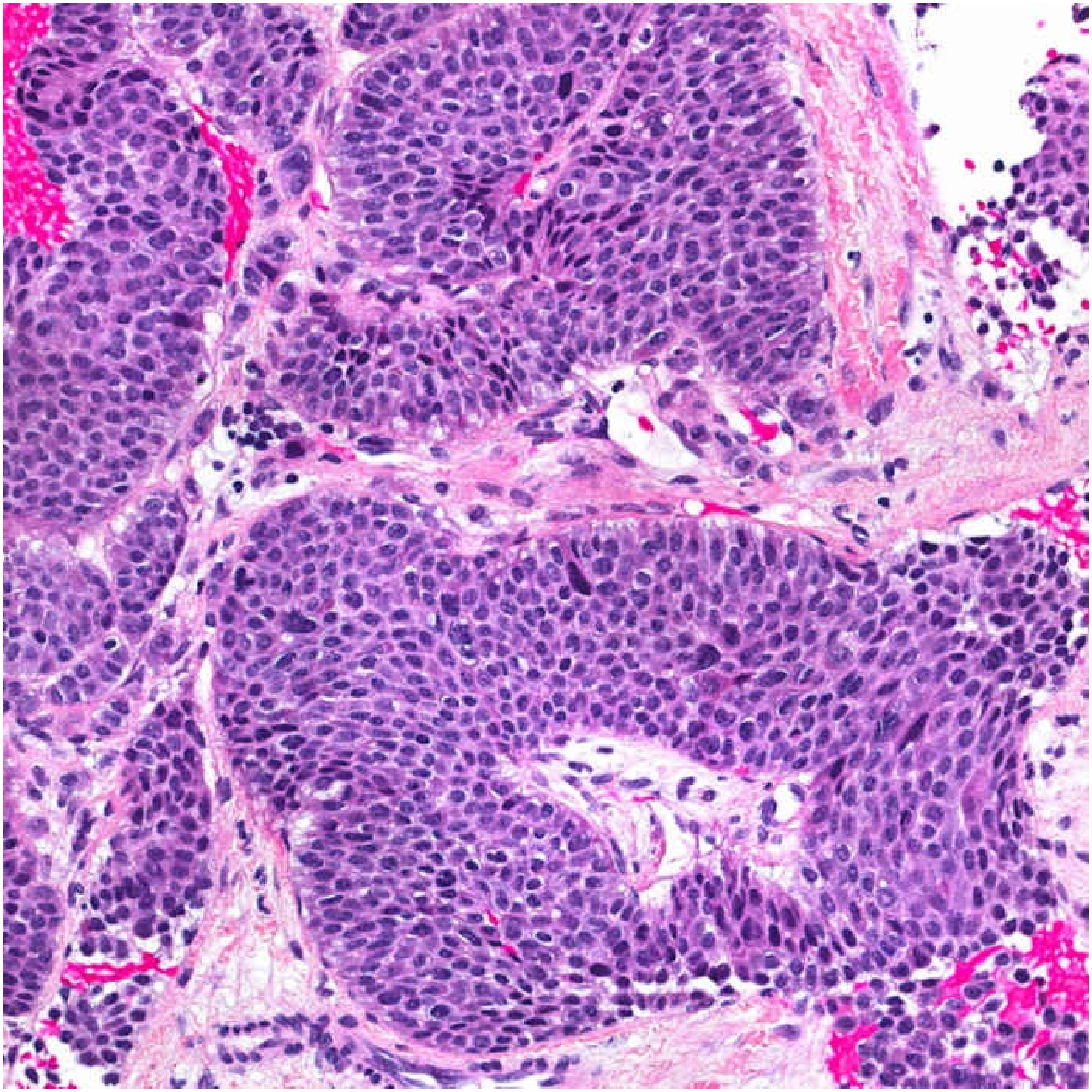

Vascular Invasion
Small cell neuroendocrine carcinoma shows necrosis and vascular invasion.



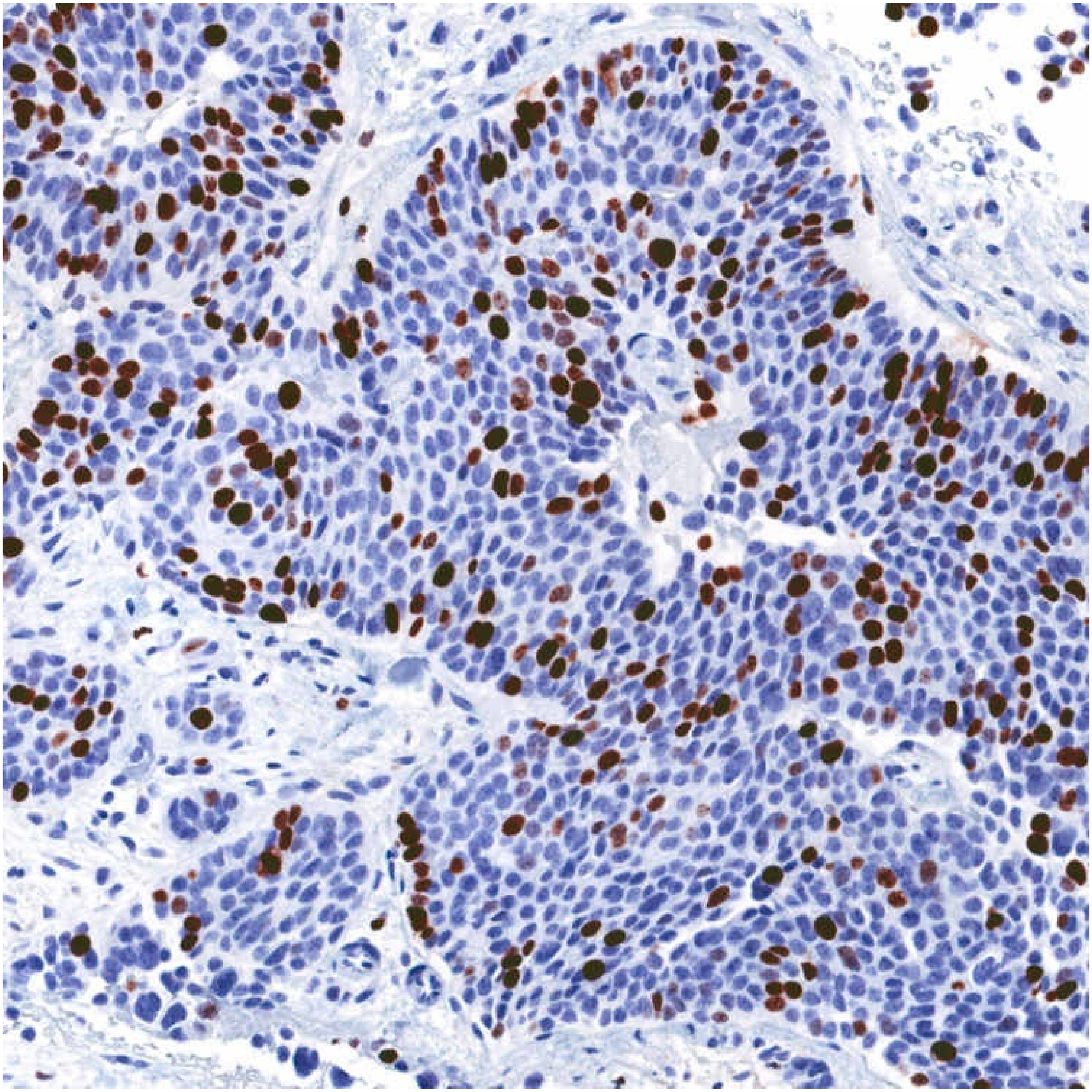
Chromogranin Stain
Large cell neuroendocrine carcinoma shows patchy staining for chromogranin. This stain has higher specificity, while synaptophysin is more sensitive for demonstrating neuroendocrine differentiation.



Mixed Adenoneuroendocrine Carcinoma
The tumor shows features of small cell neuroendocrine carcinoma →. In addition, foci of conventional adenocarcinoma are also noted in this tumor ↷. These tumors are referred to as mixed adenoneuroendocrine carcinoma as per the WHO 2010 nomenclature.



Neuroendocrine Tumor, Low-Grade Morphology
The lack of significant cytologic atypia and absence of prominent nucleoli supports a low-grade morphology.



Ki-67

Same tumor as previous image shows Ki-67 proliferation index of 22%. These tumors should not be classified as neuroendocrine carcinoma based on Ki-67 alone and are best labeled as neuroendocrine neoplasm with high proliferation index.

SELECTED REFERENCES

1. Tang, LH, et al. A practical approach to the classification of WHO grade 3 (G3) well-differentiated neuroendocrine tumor (WD-NET) and poorly differentiated neuroendocrine carcinoma (PD-NEC) of the pancreas. *Am J Surg Pathol*. 2016. [ePub].
2. Tang, LH, et al. Well-differentiated neuroendocrine tumors with a morphologically apparent high-grade component: a pathway distinct from poorly differentiated neuroendocrine carcinomas. *Clin Cancer Res*. 2016; 22(4):1011–1017.

3. Basturk, O, et al. The high-grade (WHO G3) pancreatic neuroendocrine tumor category is morphologically and biologically heterogenous and includes both well differentiated and poorly differentiated neoplasms. *Am J Surg Pathol*. 2015; 39(5):683–690.
4. Klimstra, DS, et al. The spectrum of neuroendocrine tumors: histologic classification, unique features and areas of overlap. *Am Soc Clin Oncol Educ Book*. 2015; 35:92–103.
5. Basturk, O, et al. Poorly differentiated neuroendocrine carcinomas of the pancreas: a clinicopathologic analysis of 44 cases. *Am J Surg Pathol*. 2014; 38(4):437–447.
6. Janson, ET, et al. Nordic guidelines 2014 for diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms. *Acta Oncol*. 2014; 53(10):1284–1297.
7. Reid, MD, et al. Neuroendocrine tumors of the pancreas: current concepts and controversies. *Endocr Pathol*. 2014; 25(1):65–79.
8. Yachida, S, et al. Small cell and large cell neuroendocrine carcinomas of the pancreas are genetically similar and distinct from well-differentiated pancreatic neuroendocrine tumors. *Am J Surg Pathol*. 2012; 36(2):173–184.
9. Sakamoto, H, et al. Small cell carcinoma of the pancreas: role of EUS-FNA and subsequent effective chemotherapy using carboplatin and etoposide. *J Gastroenterol*. 2009; 44(5):432–438.
10. Bismar, TA, et al. Desmoplastic small cell tumor in the pancreas. *Am J Surg Pathol*. 2004; 28(6):808–812.
11. Movahedi-Lankarani, S, et al. Primitive neuroectodermal tumors of the pancreas: a report of seven cases of a rare neoplasm. *Am J Surg Pathol*. 2002; 26(8):1040–1047.
12. Reyes, CV, et al. Undifferentiated small cell carcinoma of the pancreas: a report of five cases. *Cancer*. 1981; 47(10):2500–2502.

Well-Differentiated Neuroendocrine Tumor, Pancreas

KEY FACTS

Etiology/Pathogenesis

- Multiple endocrine neoplasia syndrome
- von Hippel-Lindau syndrome
- Tuberous sclerosis

Clinical Issues

- Surgical resection remains mainstay of therapy for tumors confined to pancreas
- Long-acting somatostatin analogs (octreotide and lanreotide) often used for metastatic tumors

Microscopic

- Monotonous population of round cells
- Exception is presence of amyloid deposits, which are indicative of insulinoma
- Features associated with adverse outcome include size > 2 cm, necrosis, vascular invasion, perineural invasion, tumor grade

Ancillary Tests

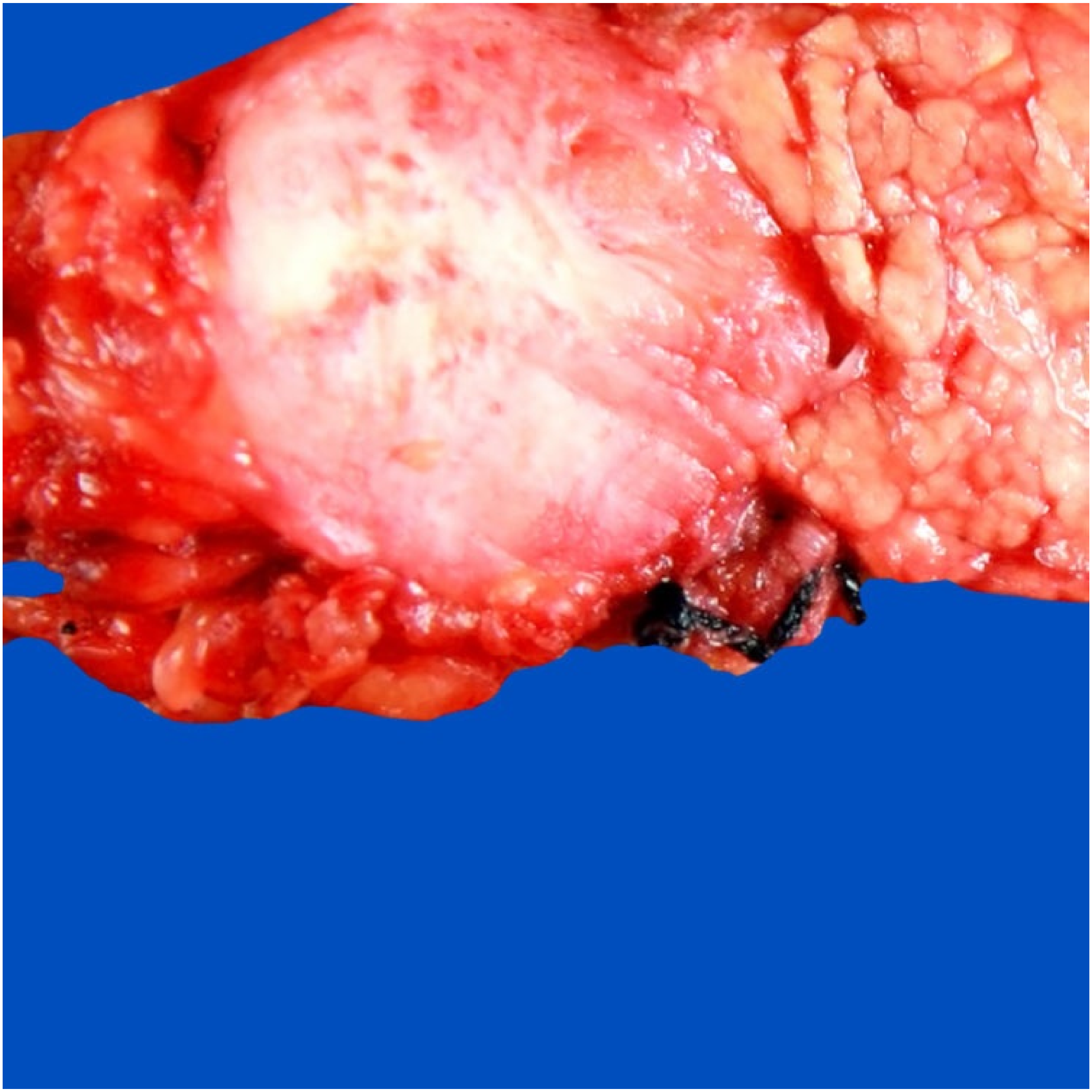
- Chromogranin and synaptophysin
- Immunohistochemistry for peptide hormones
- Immunohistochemistry not reliable to determine pancreatic origin for metastatic tumors

Top Differential Diagnoses

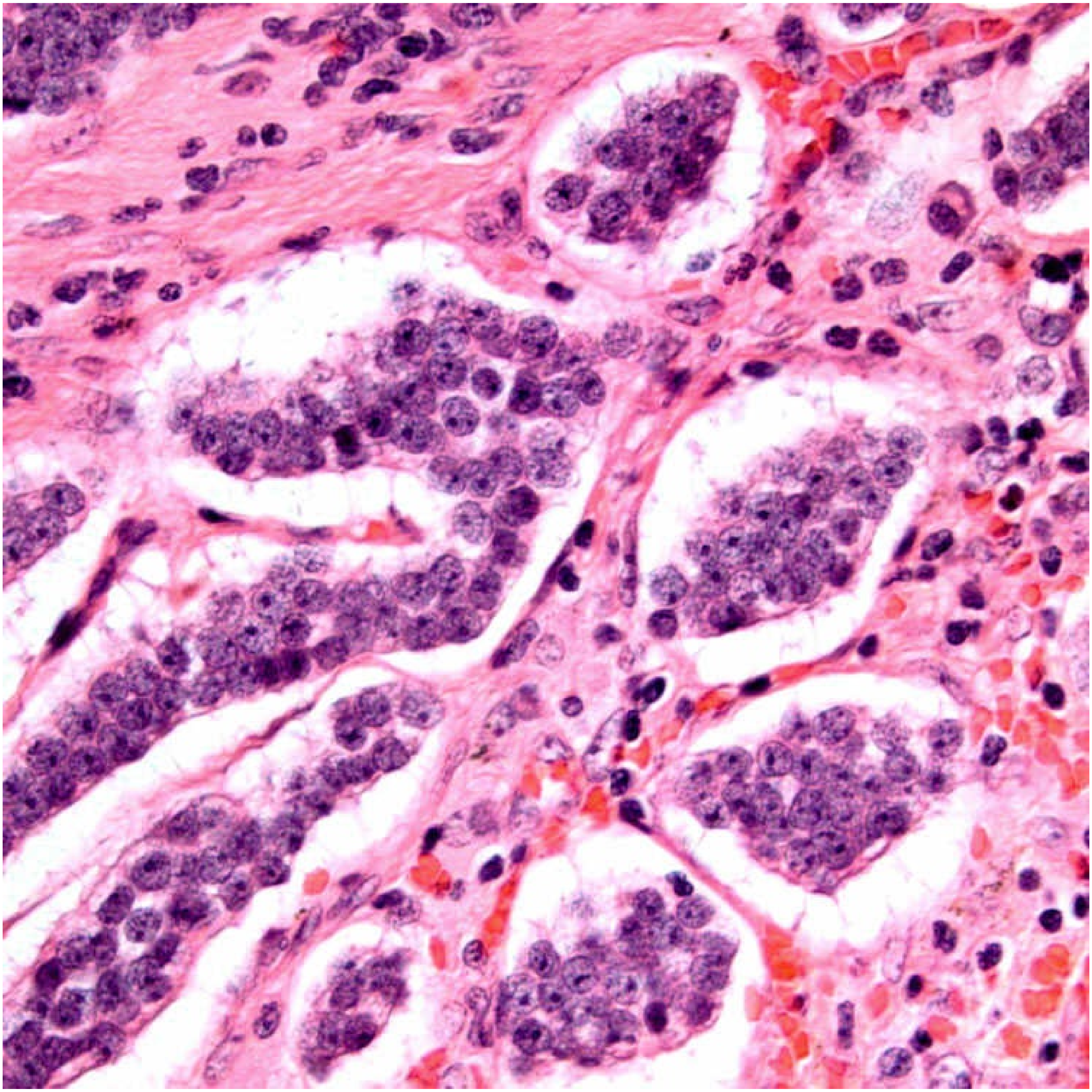
- Acinar cell carcinoma
- Solid pseudopapillary neoplasm
- Neuroendocrine carcinoma

Grading

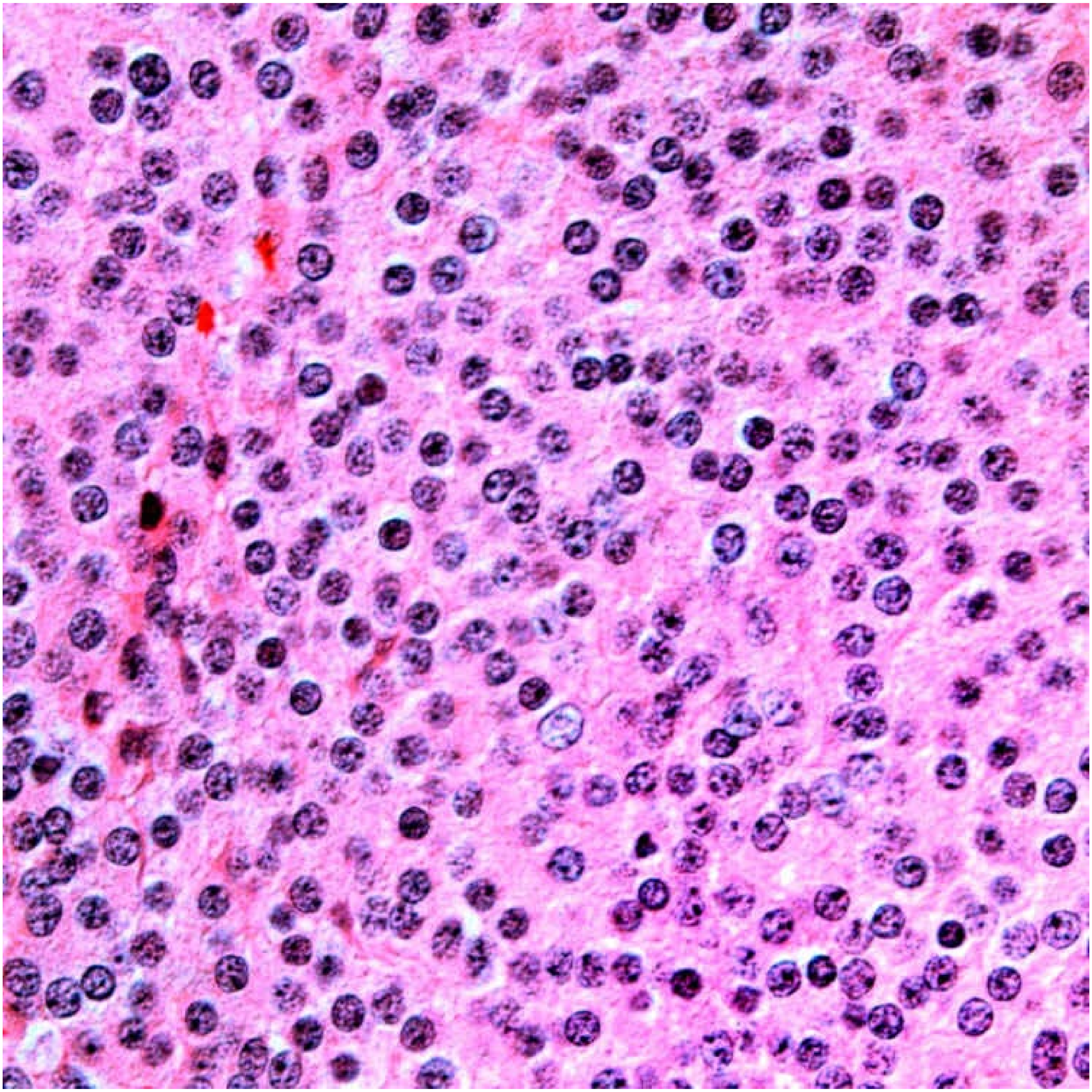
- Grade 1 (low grade)
- Mitoses < 2 per 10 HPF &/or Ki-67 index < 3%
- Grade 2 (intermediate grade)
- Mitoses 2-20 per 10 HPF &/or Ki-67 index 3-20%



Pancreatic Neuroendocrine Tumor
A well-circumscribed solid mass in the pancreas is typical of low-grade neuroendocrine tumors.

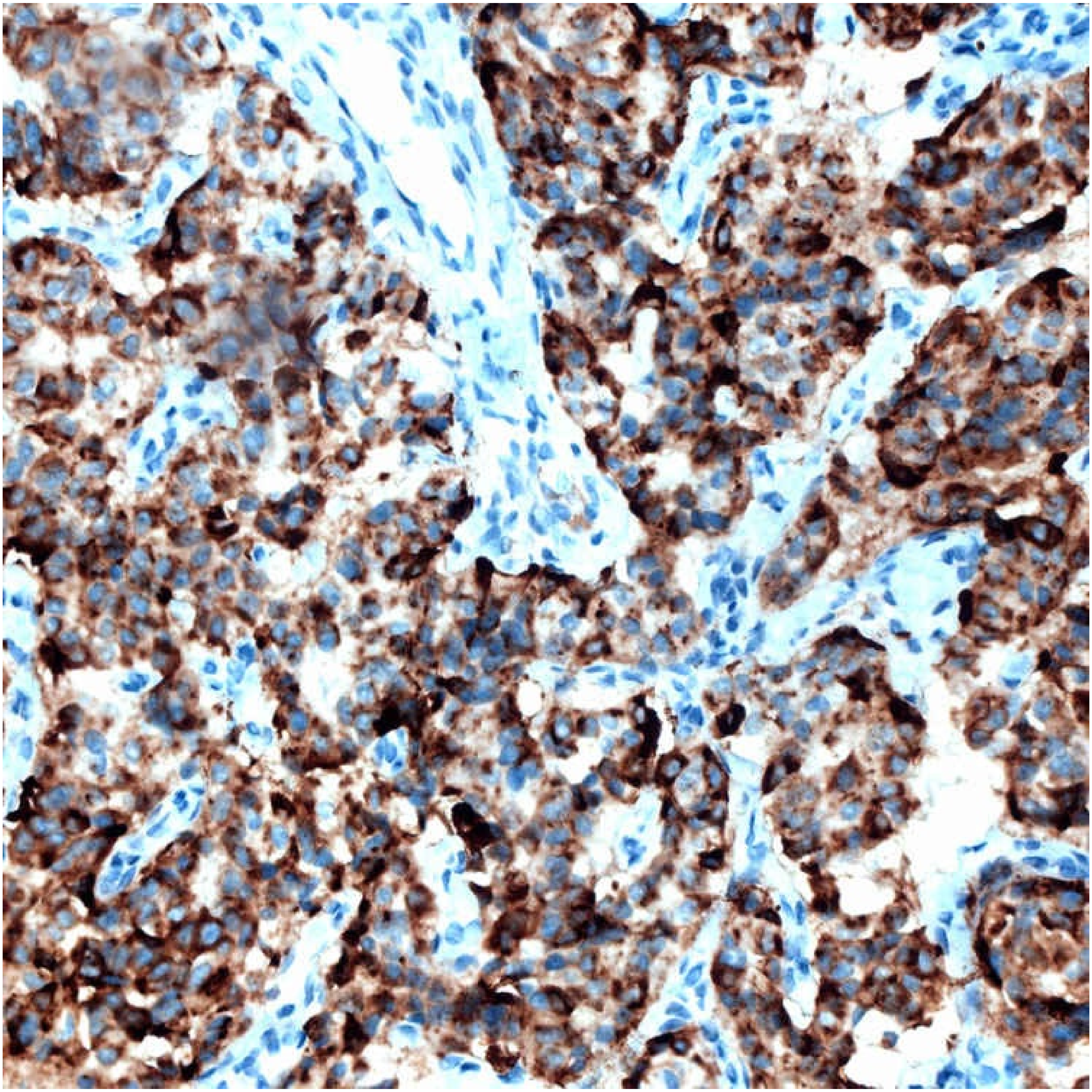


Nested Architecture
The tumor cells show a nested pattern of growth. The individual tumor cells have uniform nuclei, small nucleoli, and lack prominent nuclear atypia, mitoses, or necrosis.



Solid Growth Pattern

The solid growth pattern and round monotonous nuclei support pancreatic neuroendocrine tumors, but immunohistochemistry is required to distinguish them from solid pseudopapillary tumors and acinar cell carcinomas.



Chromogranin Stain
Diffuse positive staining is shown. Absence of reactivity for neuroendocrine markers (chromogranin/synaptophysin) should prompt reevaluation of the diagnosis.

TERMINOLOGY

Abbreviations

- Neuroendocrine tumor (NET)

Synonyms

- Pancreatic NET

- Pancreatic endocrine tumor
- Islet cell tumor

Definitions

- Low- to intermediate-grade NET of pancreas

ETIOLOGY/PATHOGENESIS

Syndromic

- Multiple endocrine neoplasia syndrome
- von Hippel-Lindau syndrome
- Tuberous sclerosis

Sporadic

- Majority of cases are nonsyndromic and sporadic

CLINICAL ISSUES

Presentation

- Epidemiology
  - Peak incidence between 30-60 years
  - No significant gender predilection
- Presenting symptoms
  - Abdominal pain, jaundice
  - Asymptomatic, detected by imaging
    - Such incidentally detected pancreatic NETs are increasingly common
- Endocrine function
  - Functioning tumors
    - Insulinoma
    - Glucagonoma
    - Somatostatinoma
    - Gastrinoma
    - Vipomas
  - Nonfunctional tumors
    - More common than functional tumors

Treatment

- Surgical approaches
  - Surgical resection remains mainstay of therapy for tumors confined to pancreas
  - Enucleation is restricted to small tumors (typically < 2 cm)

- Options for tumors metastatic to liver
  - Resection of primary and surgical debulking of metastatic tumor
  - Long-acting somatostatin analogs (octreotide and lanreotide)
  - Liver-directed therapy, including embolization, chemoembolization, radiofrequency ablation
  - Novel agents, such as inhibitor of VEGF, inhibitor of tyrosine kinase, and mTOR pathway

Prognosis

- Outcome is variable
  - Histological and immunohistochemical features help estimate risk of aggressive behavior
  - Features associated with adverse outcome include
  - Size > 2 cm
  - Tumor necrosis
  - Mitoses > 2/10 HPF
  - Vascular invasion
  - Perineural invasion
  - High Ki-67 index
  - CK19 positivity

IMAGING

CT Findings

- Solid, or less commonly, solid and cystic, well-circumscribed, enhancing lesion

MACROSCOPIC

General Features

- Solid, round to oval, well-circumscribed mass
  - ~ 5% of tumors are cystic
  - Either multilocular or unicystic

Size

- Tumors < 0.5 cm are termed microadenomas

MICROSCOPIC

Histologic Features

- Monotonous population of round cells
  - Nuclear chromatin is typically coarse with salt and pepper appearance
  - Large nucleoli may be present
  - Less common cytoplasmic variations include oncocytic, vacuolated lipid-rich variant, and rhabdoid
  - Morphological appearance generally does not predict functional status
  - Exception is presence of amyloid deposits, which are indicative of insulinoma

ANCILLARY TESTS

Immunohistochemistry

- Chromogranin and synaptophysin
  - Diffusely and strongly positive
  - Chromogranin is more specific, while synaptophysin has higher sensitivity
  - Positive staining with 1 of these 2 markers is essential for diagnosis
- CD56, CD57 may be positive but are not specific for neuroendocrine differentiation
- Cytokeratins
  - Pankeratin is usually positive
  - Keratins 8 and 18 are positive, while 7 and 19 are positive in most cases
- Ki-67
  - Used for grading of NETs along with mitotic count
- Immunohistochemistry for peptide hormones
  - Rarely required for diagnosis
  - Nonfunctional tumors may stain for multiple peptides
- Marker for pancreatic NETs in metastatic setting
  - ISL1 positivity would support primary pancreatic NET
  - pax-8 is positive in 50-60% of metastatic pancreatic NETs metastatic to liver
  - TTF-1 is negative in pancreatic NETs, while CDX-2 is negative or patchy positive
  - Immunohistochemistry is not reliable to determine pancreatic origin

DIFFERENTIAL DIAGNOSIS

Acinar Cell Carcinoma

- Acinar pattern suggests acinar cell carcinoma
- Prominent nucleoli and high mitotic activity
- Cytoplasmic PAS-positive diastase-resistant granules can be present
- Immunohistochemistry: Tumor cells are positive for trypsin

Solid Pseudopapillary Neoplasm

- Pseudopapillary pattern rare in NETs
- Distinctive nuclear features: Oval with fine, evenly distributed chromatin and longitudinal nuclear grooves
- Immunohistochemistry: Nuclear β-catenin, loss of membranous E-cadherin staining, CD10, progesterone receptor
- Synaptophysin can be positive, but chromogranin is negative

Neuroendocrine Carcinoma

- Mitoses > 20 per 10 HPF &/or Ki-67 index > 20%
- Can be large cell or small cell

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Functional tumors defined on basis of clinical symptoms, not immunohistochemical findings

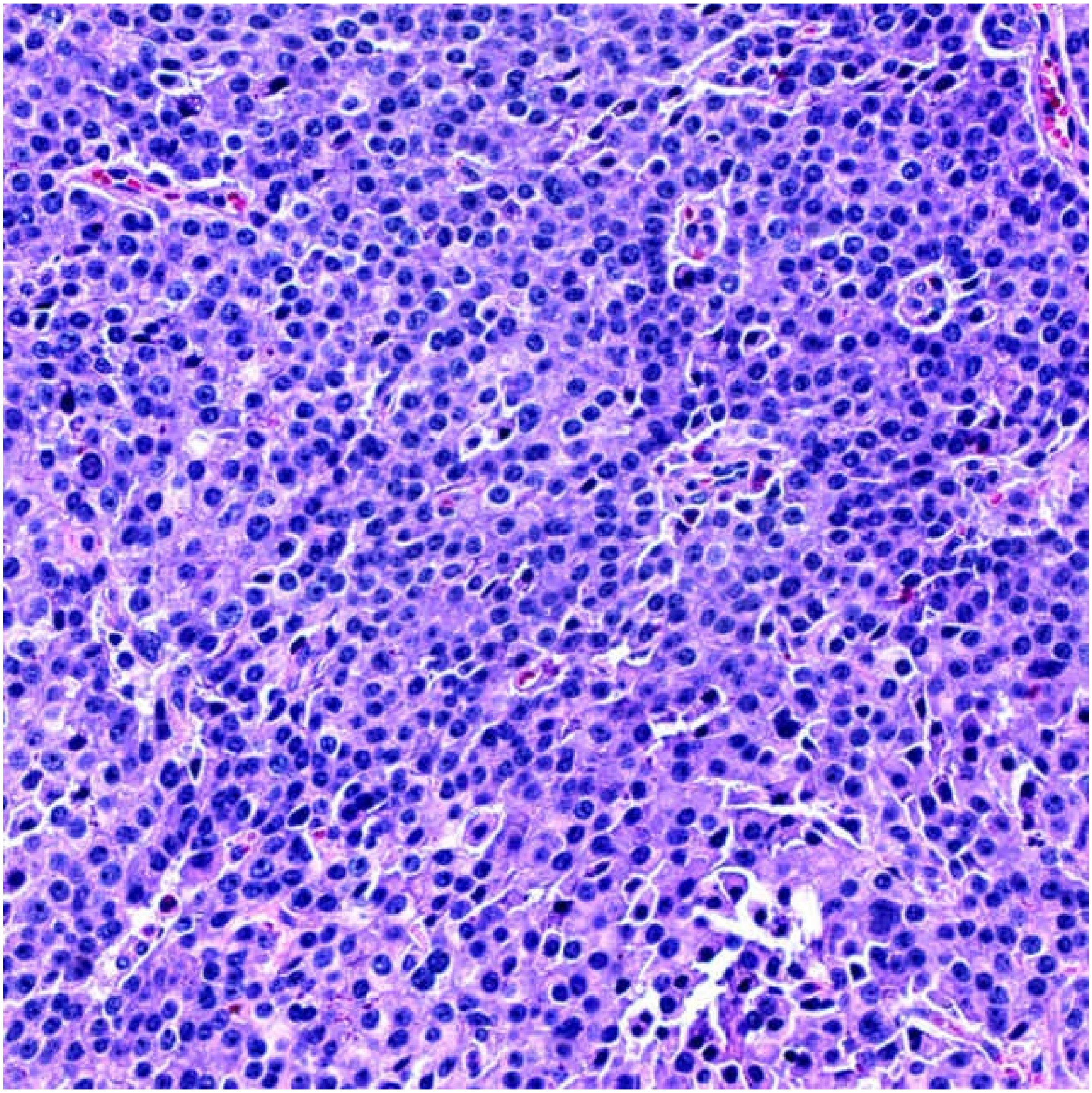
Pathologic Interpretation Pearls

- Multiple endocrine tumors suggest syndrome, such as multiple endocrine neoplasia syndrome and von Hippel-Lindau syndrome
- Rarely, tumors < 2 cm and without aggressive features may metastasize

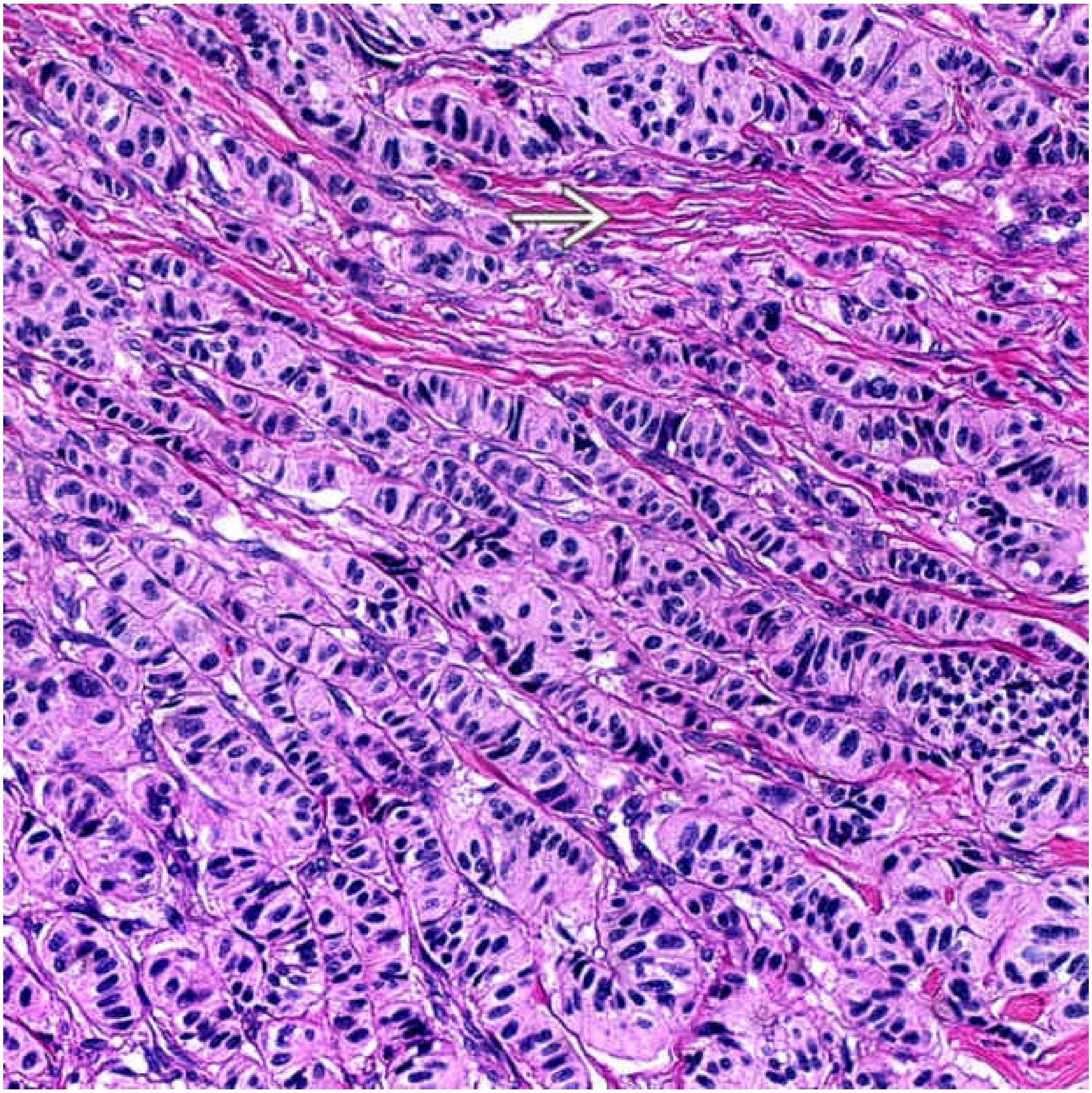
GRADING

Pancreatic Neuroendocrine Neoplasms (WHO 2010)

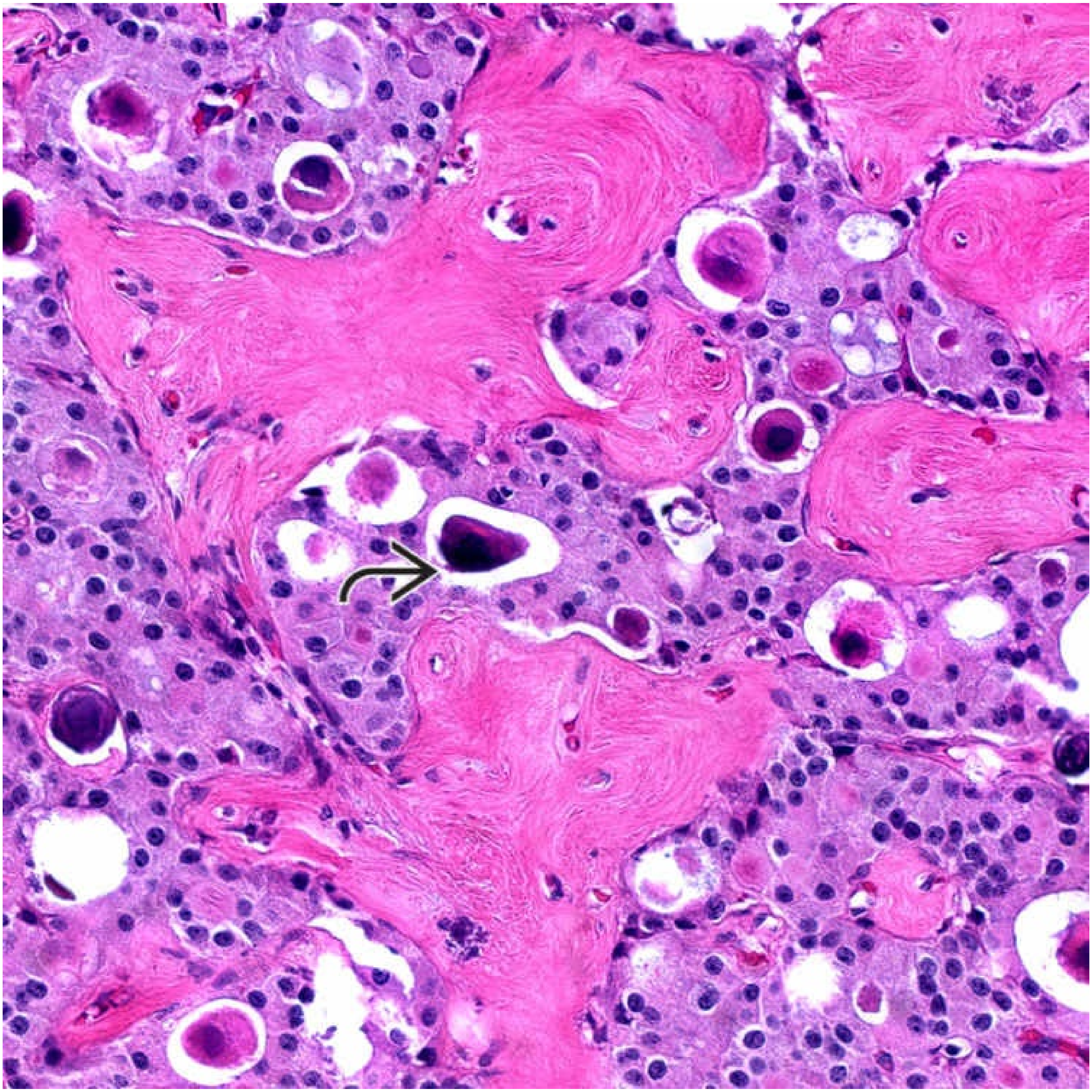
- Grade 1 (low grade)
  - Mitoses < 2 per 10 HPF &/or Ki-67 index < 3%
- Grade 2 (intermediate grade)
  - Mitoses 2-20 per 10 HPF &/or Ki-67 index 3-20%
- Grade 3 (neuroendocrine carcinoma)
  - Mitoses > 20 per 10 HPF &/or Ki-67 index > 20%
    - Mitotic count should be based upon counting 50 HPF (40x objective) in area of highest mitotic activity and reported as number of mitoses per 10 HPF (1 HPF = 2 mm^2)
    - Ki-67 index: Percentage of positive tumor cells in area of highest nuclear labeling based on 500-2000 tumor cells
    - Discordance between mitoses and Ki-67 in grading of low-grade NETs is seen in 1/3 of cases
    - Preliminary evidence suggests discordant cases that are grade 2 based on mitoses and Ki-67 tend to be more aggressive than NET grade 1 concordant cases
    - In rare cases, tumors with low-grade morphology may have Ki-67 index of > 20%
      - Natural history of these tumors is unclear, and it is prudent to report these descriptively as neuroendocrine neoplasms with high Ki-67 index
      - Outcome is intermediate between typical low-grade NET and typical high-grade neuroendocrine carcinoma
      - Unlike high-grade neuroendocrine carcinomas, platinum-based therapy is not effective in these cases



Solid Growth Pattern
Pancreatic neuroendocrine tumor with a solid growth pattern is shown.

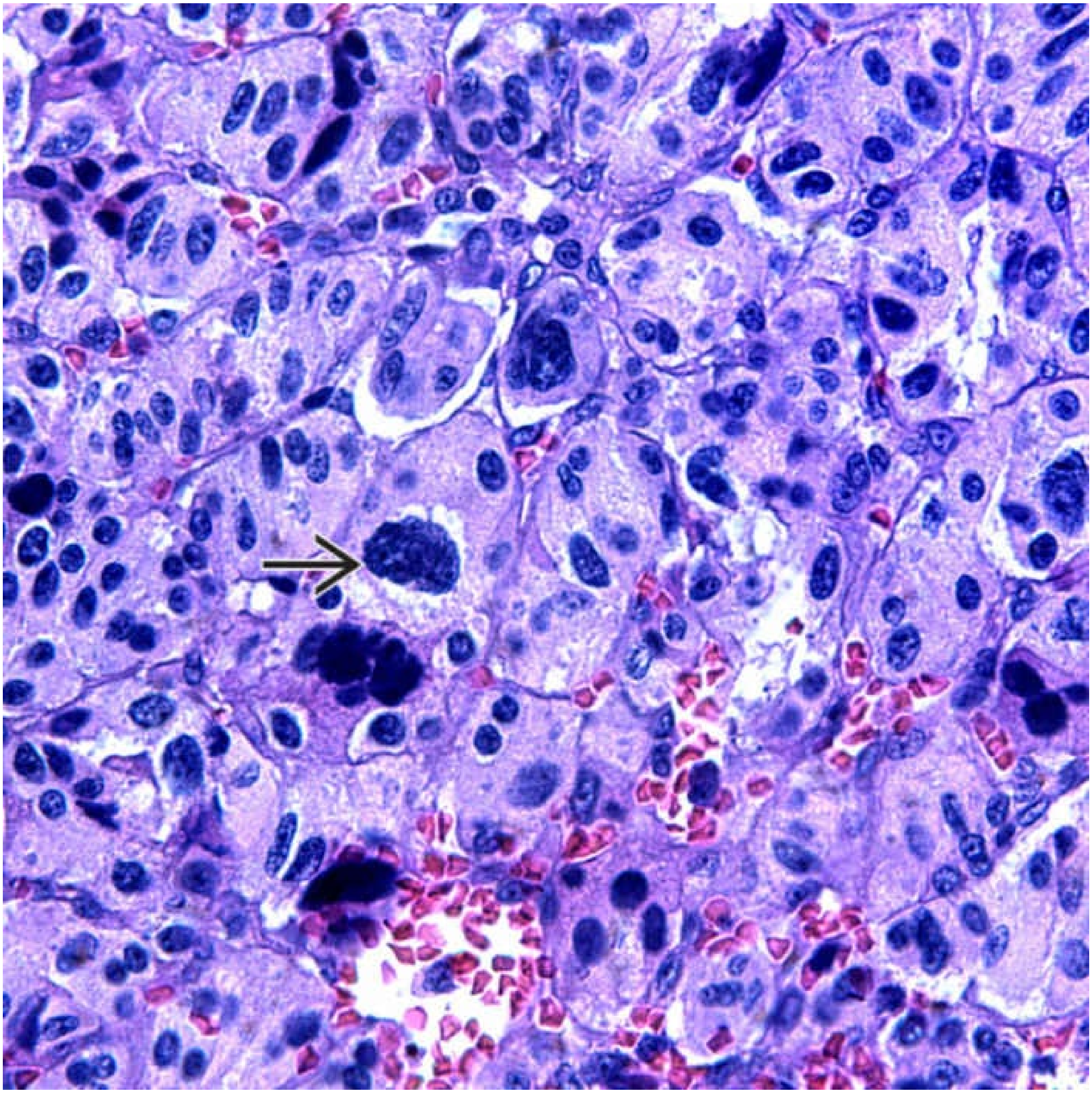


Trabecular Architecture
Pancreatic neuroendocrine tumor with prominent trabecular architecture is shown. The monotony of the cells suggest neuroendocrine cell differentiation. Scant collagenous stroma is present ⇒. Some pancreatic neuroendocrine tumors may show abundant stroma.



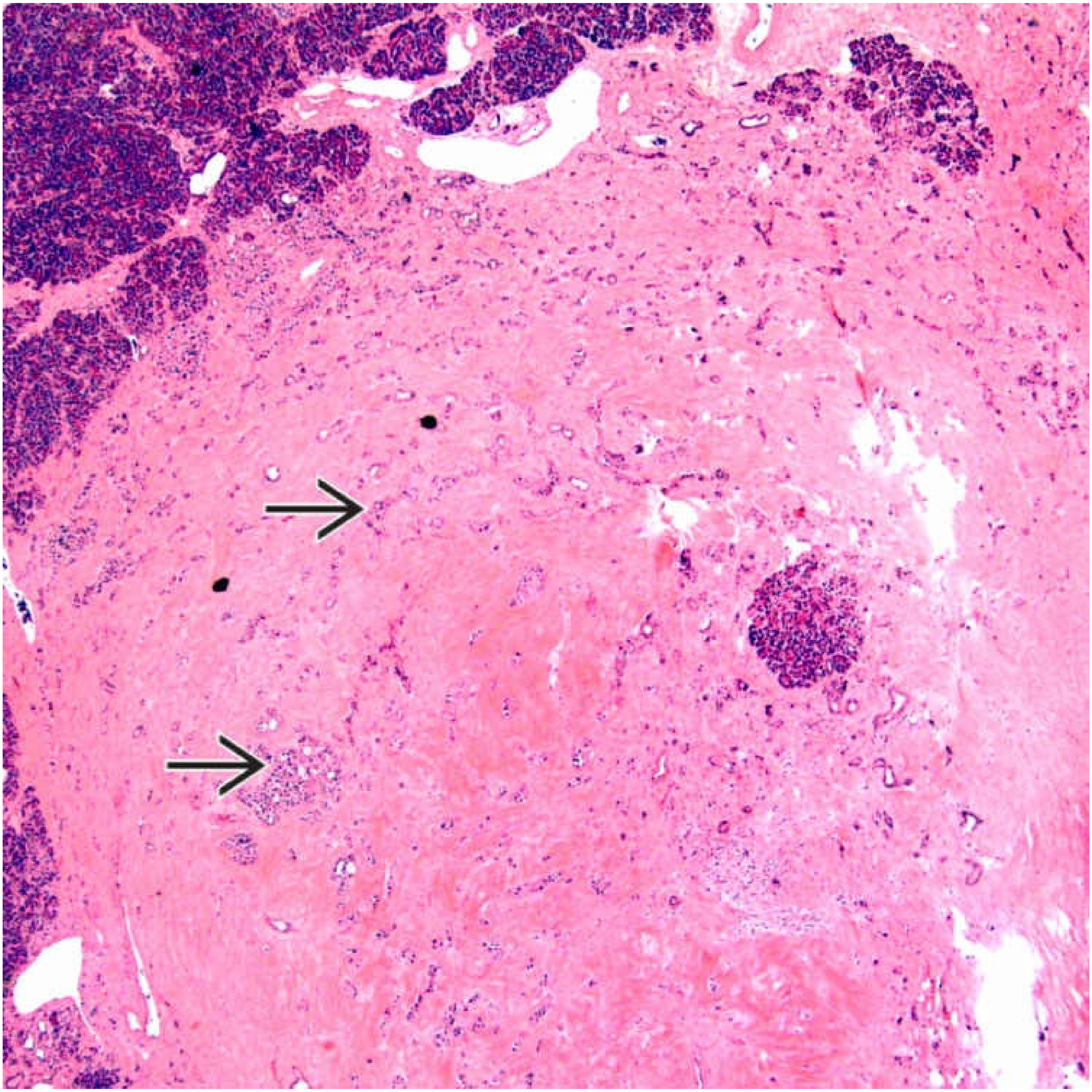
Acinar Architecture

Pancreatic neuroendocrine tumor with prominent acinar pattern and intraluminal calcifications ↷ is shown. On immunohistochemistry, the tumor was positive for insulin.

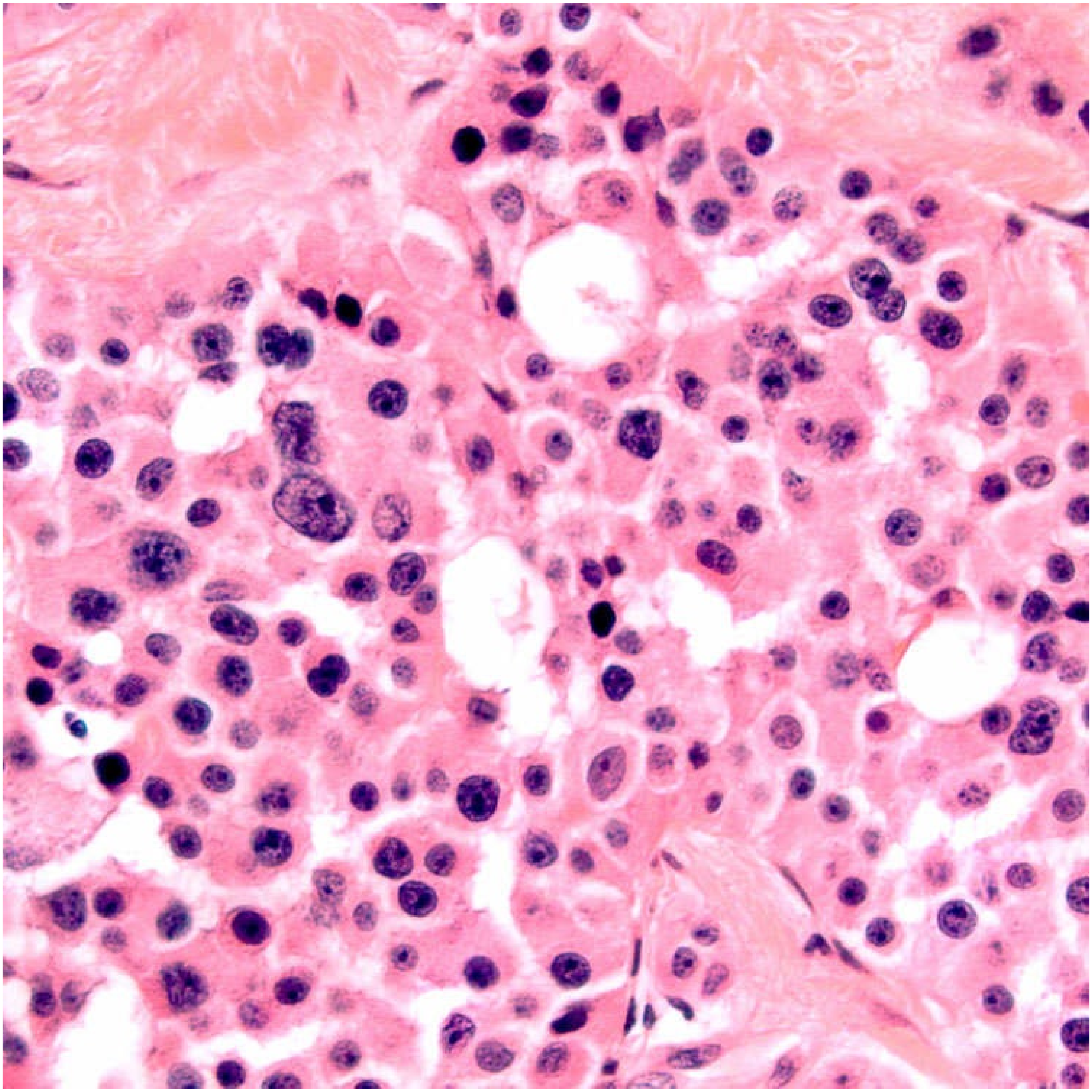


Nuclear Pleomorphism

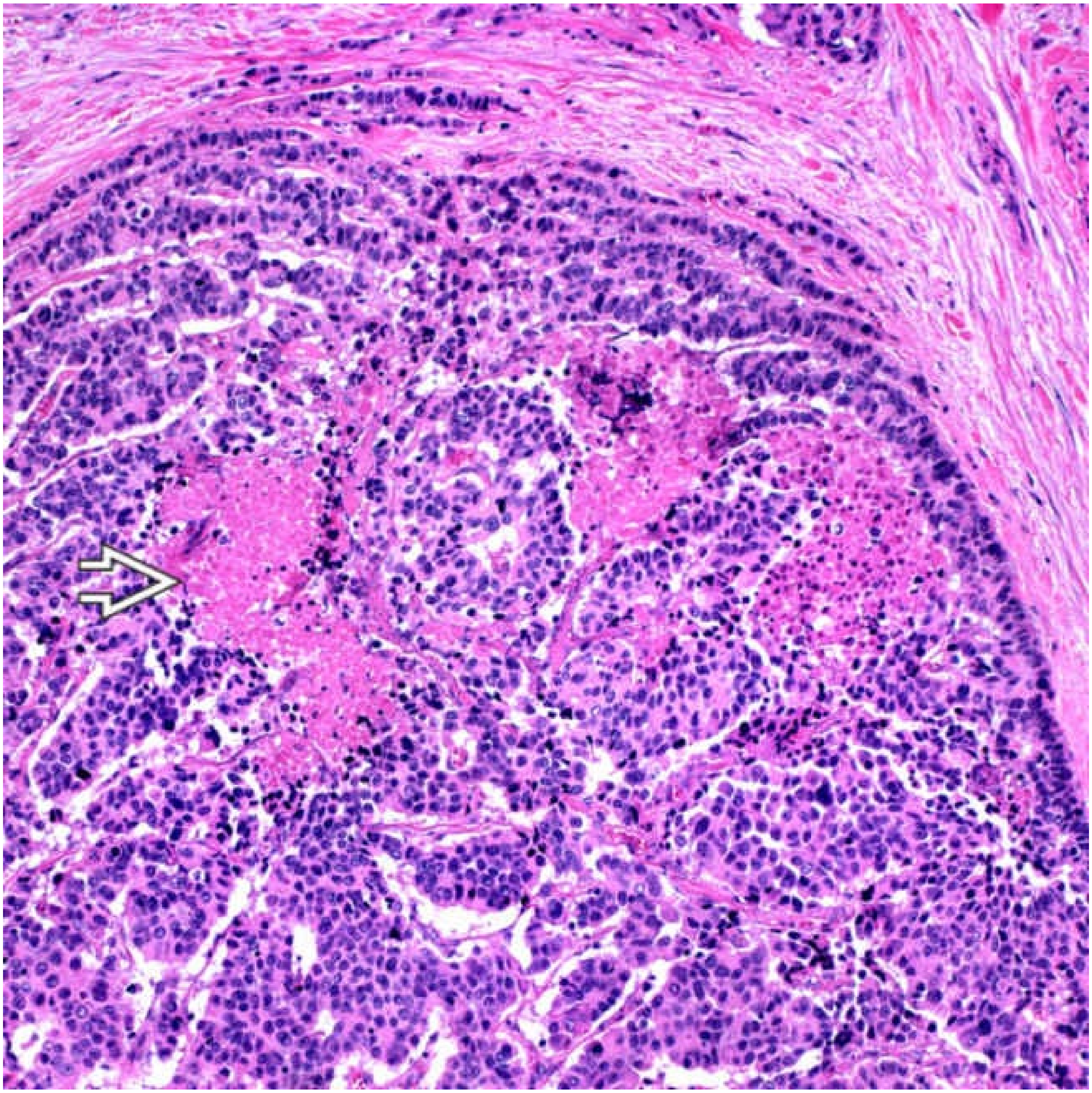
Marked pleomorphism → is occasionally seen and is not clinically significant. The enlarged nuclei have a smudged chromatin and represent a degenerative phenomenon. The remaining tumor shows typical features of low-grade NET.



Hyalinized Stroma
Abundant hyalinized stroma and entrapped nests of tumor cells → are shown. The area of hyalinization usually represents collagen, but amyloid can be present.

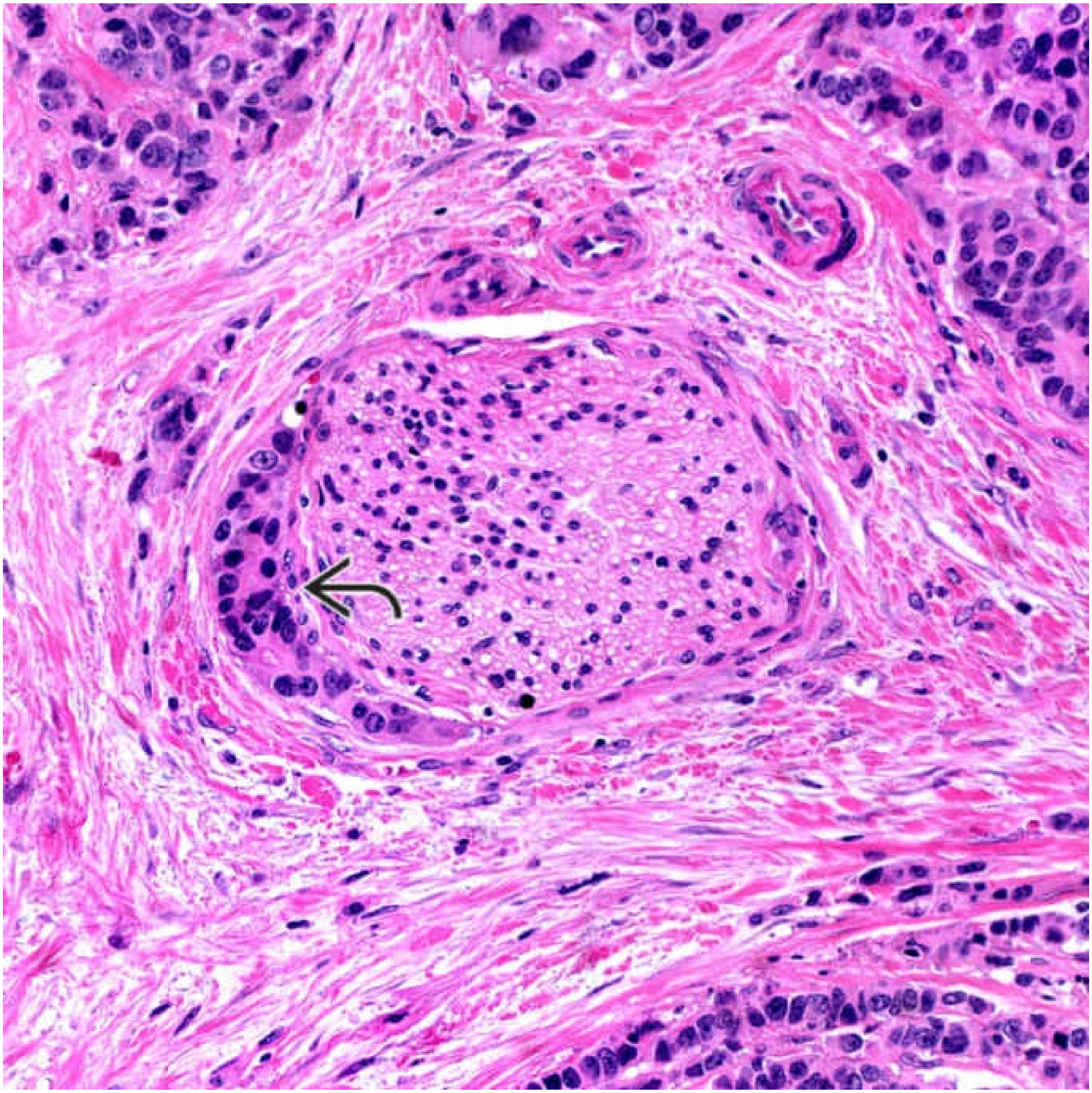


Oncocytic Change
Pancreatic neuroendocrine tumor is seen with abundant eosinophilic granular cytoplasm (oncocytic change), which is often related to prominent mitochondria in cytoplasm of tumor cells.



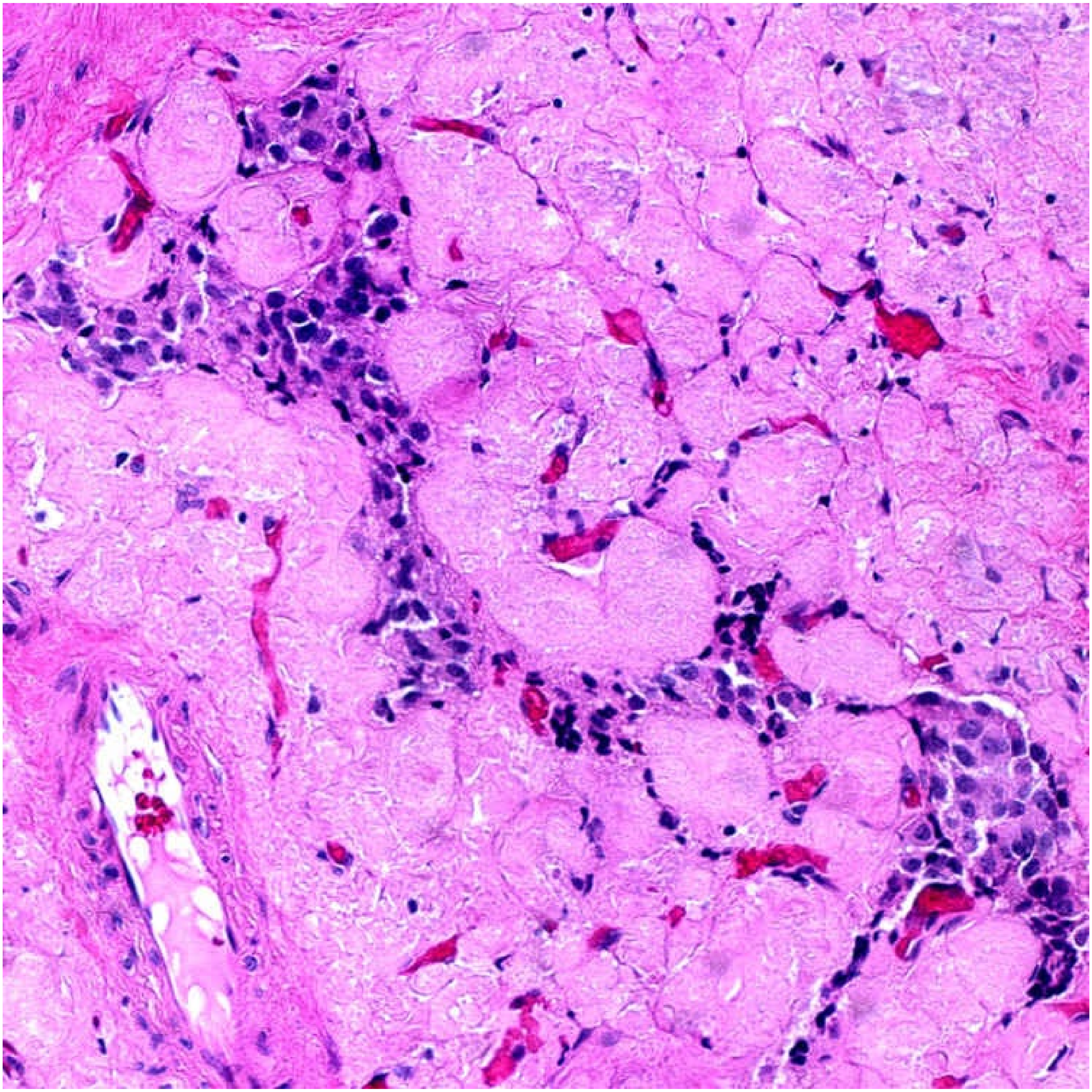
Necrosis

Punctate foci of necrosis ⇨ are shown in a low-grade neuroendocrine tumor. Necrosis does not influence the tumor grade in the WHO 2010 grading scheme.

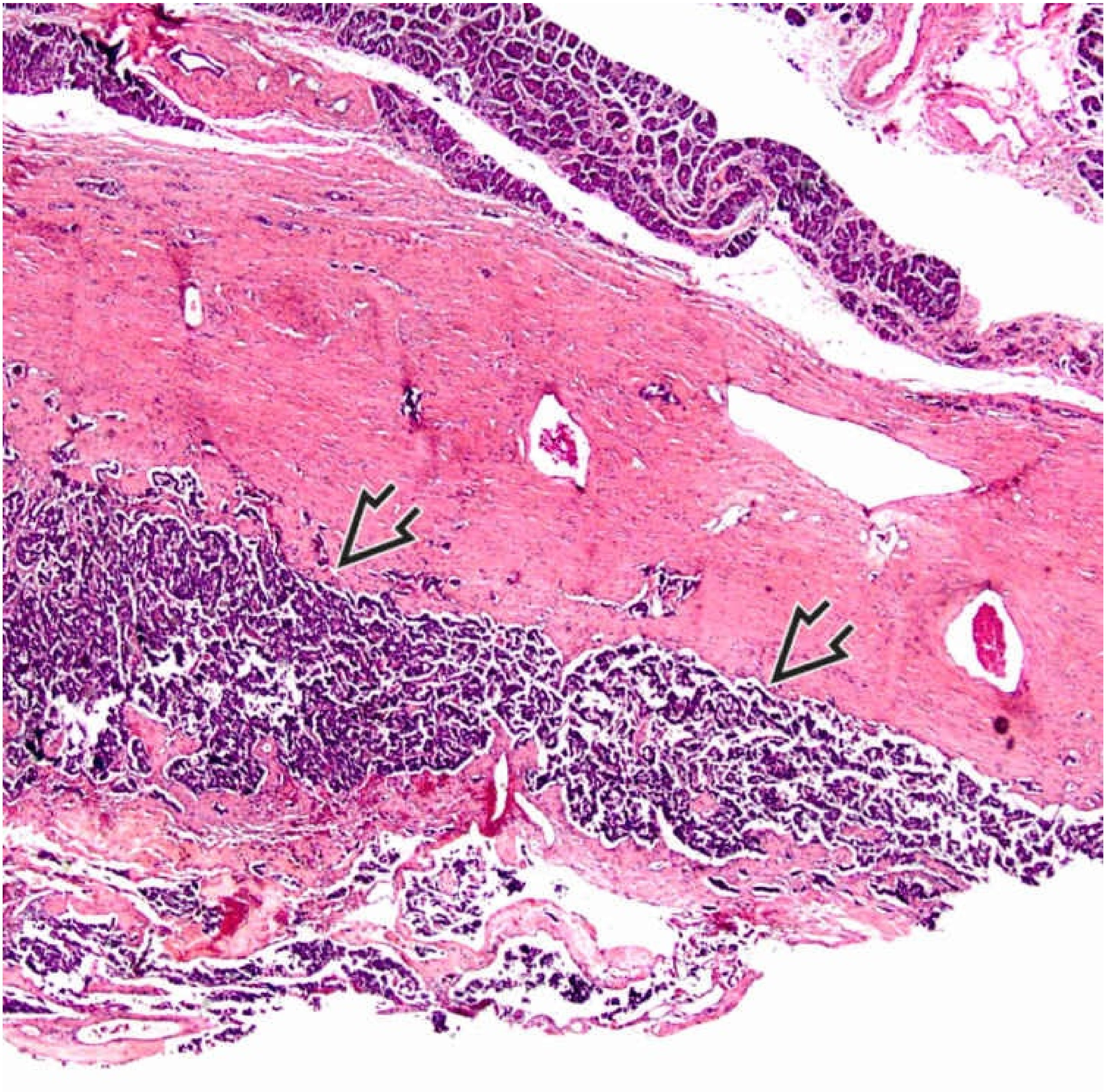


Perineural Invasion

Perineural invasion, like tumor necrosis, is predictive of aggressive behavior. This histologic feature is not part of the WHO 2010 grading scheme.

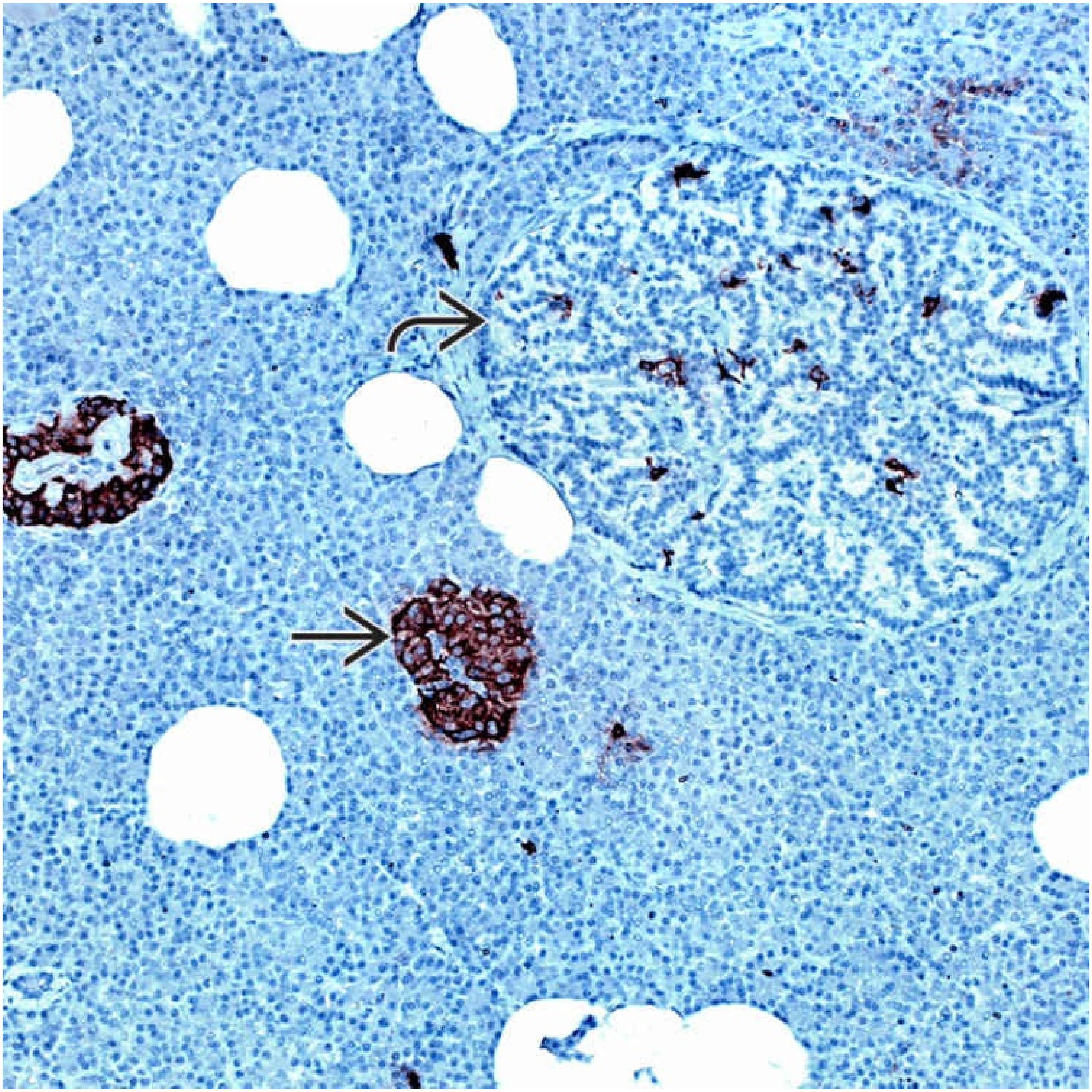


Amyloid Deposits
Abundant extracellular, amorphous eosinophilic material typical of amyloid is observed in the stroma of the tumor. The amyloid is composed of islet amyloid polypeptide.



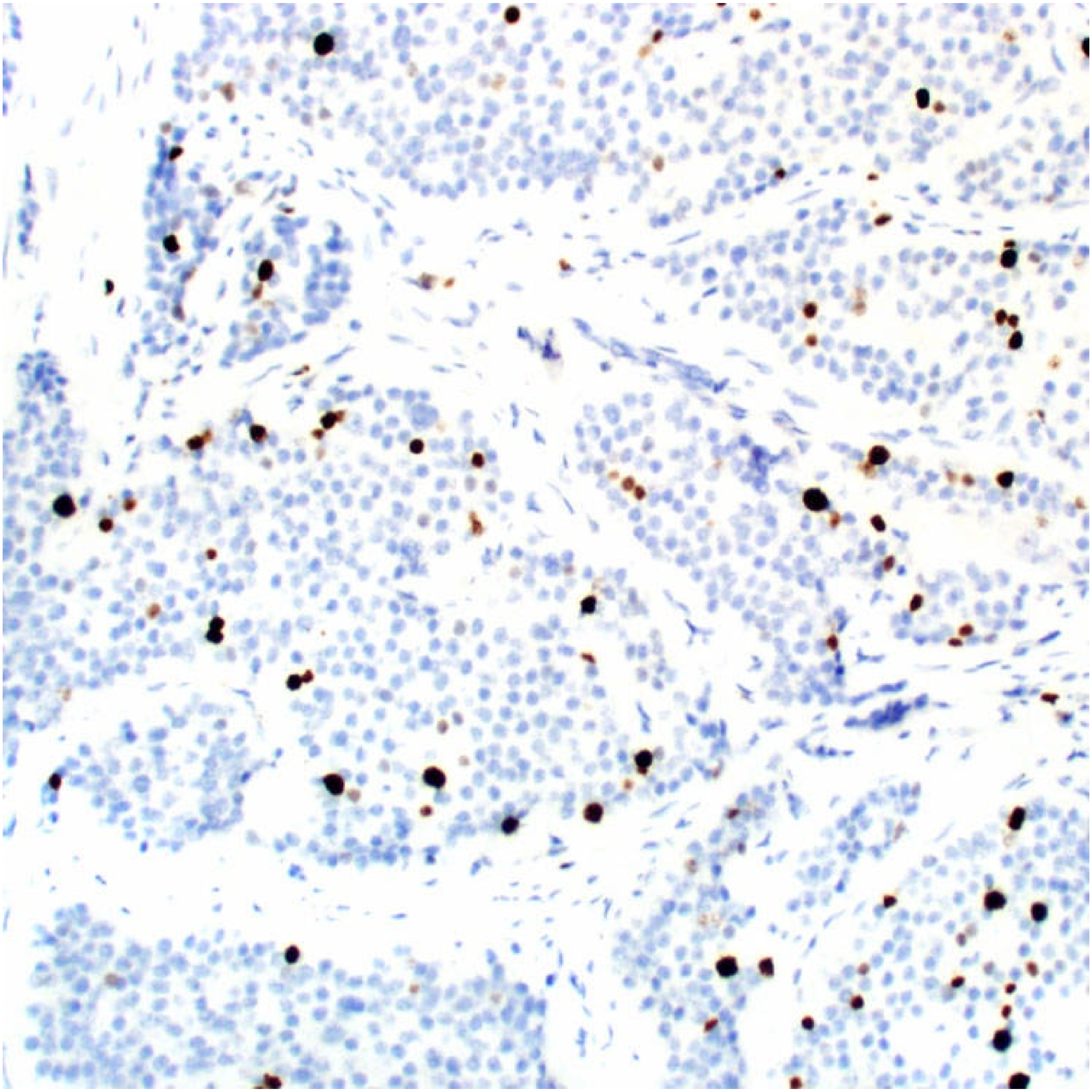
Cystic Change

Pancreatic neuroendocrine tumor presenting as a unilocular cyst without a mural nodule is shown. A thin layer of tumor is compressed along the fibrous cyst wall. These tumors can be mistaken for benign cysts.

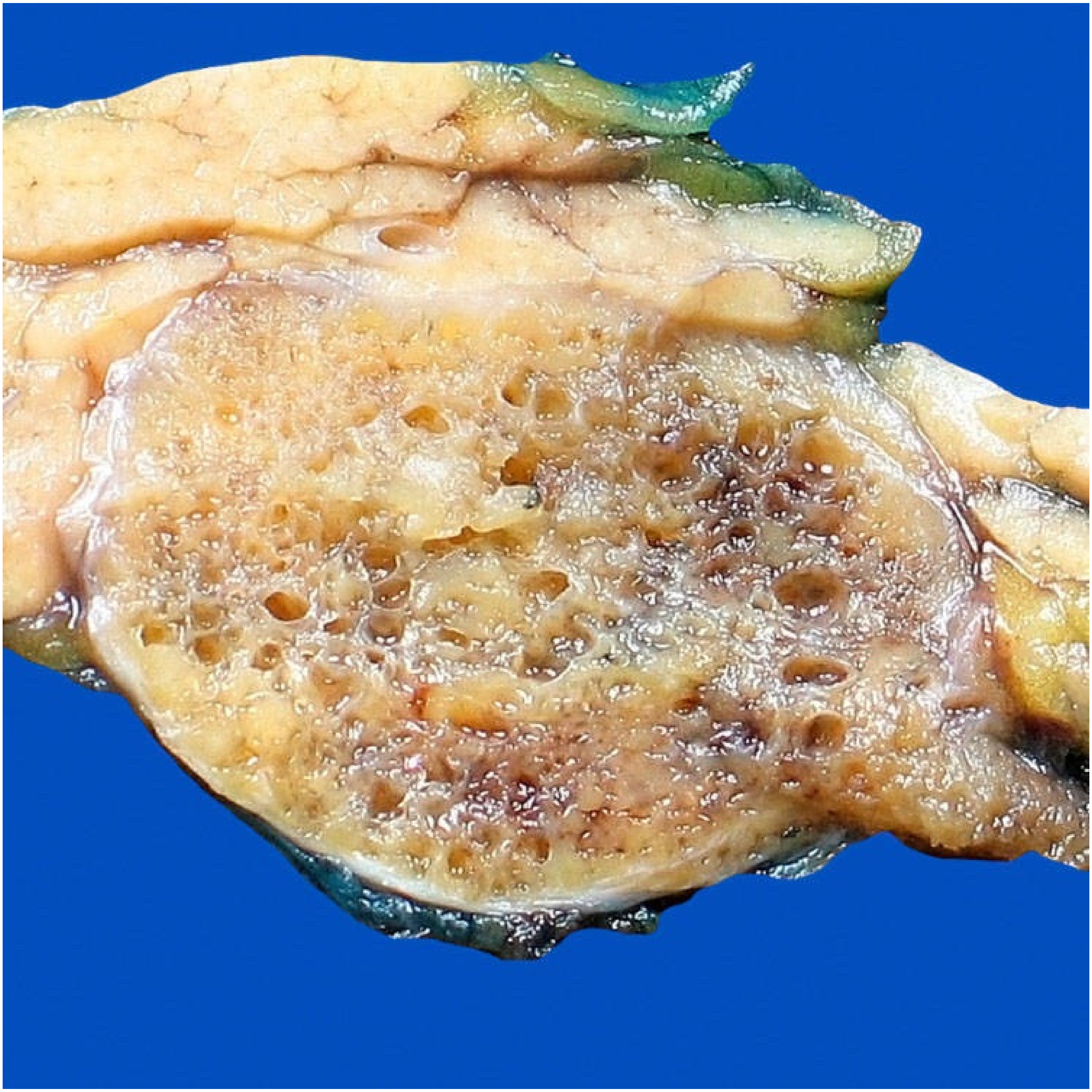


Pancreatic Microadenoma

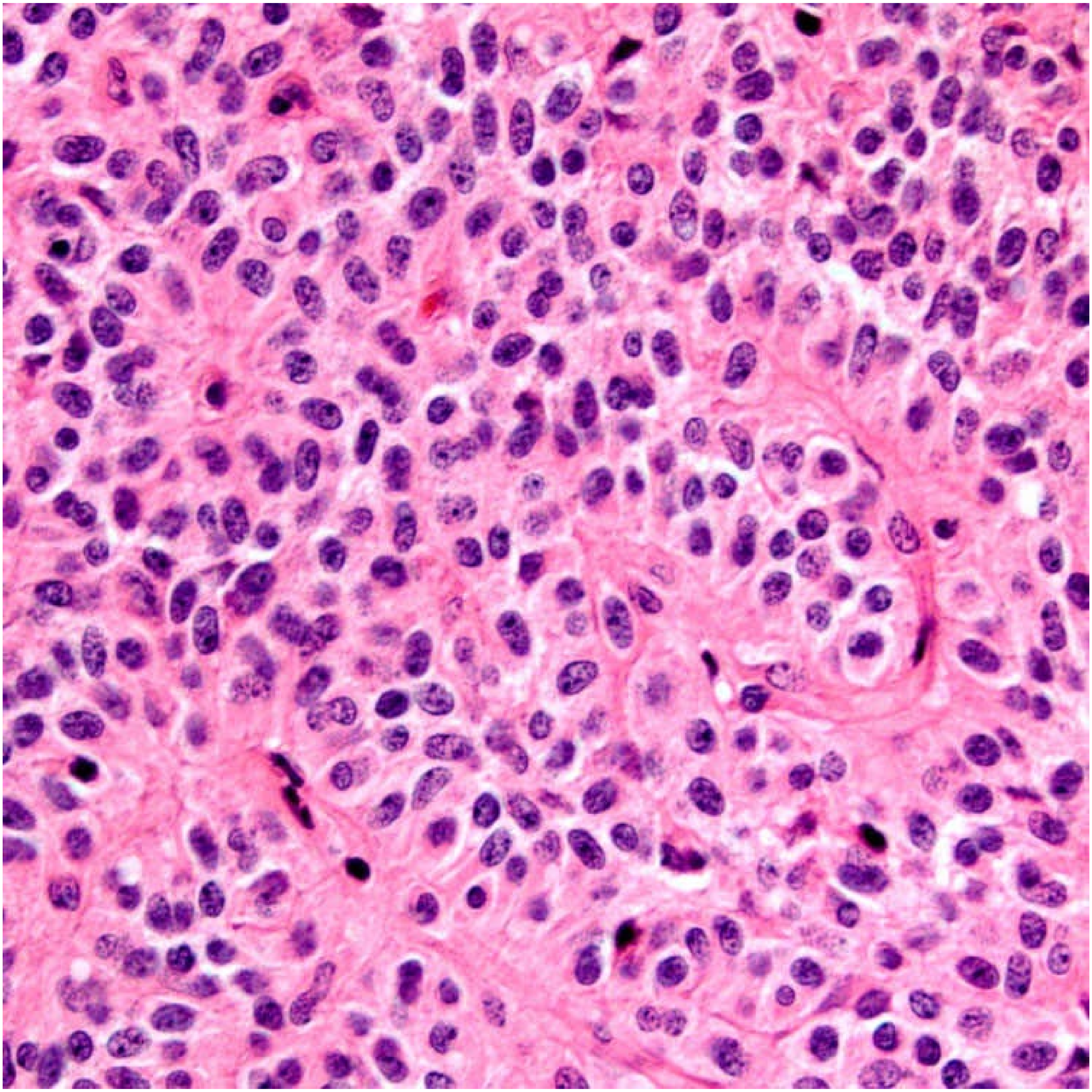
Pancreatic microadenoma ↱ in multiple endocrine neoplasia syndrome is shown. In contrast to normal islets →, microadenomas show only focal insulin reactivity. Large numbers of microadenomas are seen in multiple endocrine neoplasia syndrome.



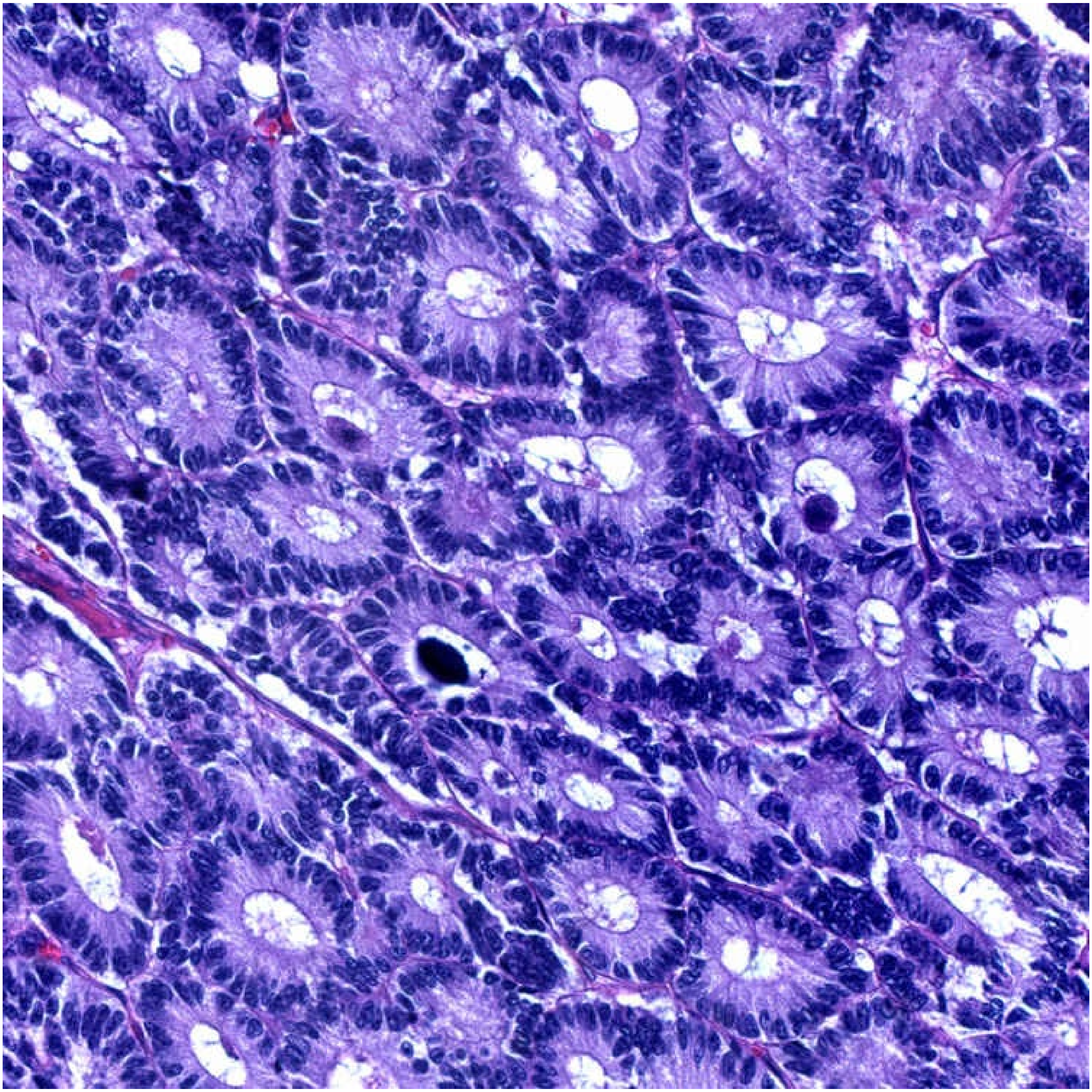
Ki-67 Immunohistochemistry
Immunohistochemistry for Ki-67 is necessary to determine the accurate grade. In this tumor, the mitotic rate was < 2 per 10 HPF, but the Ki-67 proliferation index of 8% indicates that this is a grade 2 neuroendocrine tumor.



Pancreatic Neuroendocrine Tumor
Pancreatic neuroendocrine tumor with a microcystic appearance mimicking serous cystadenoma is shown.

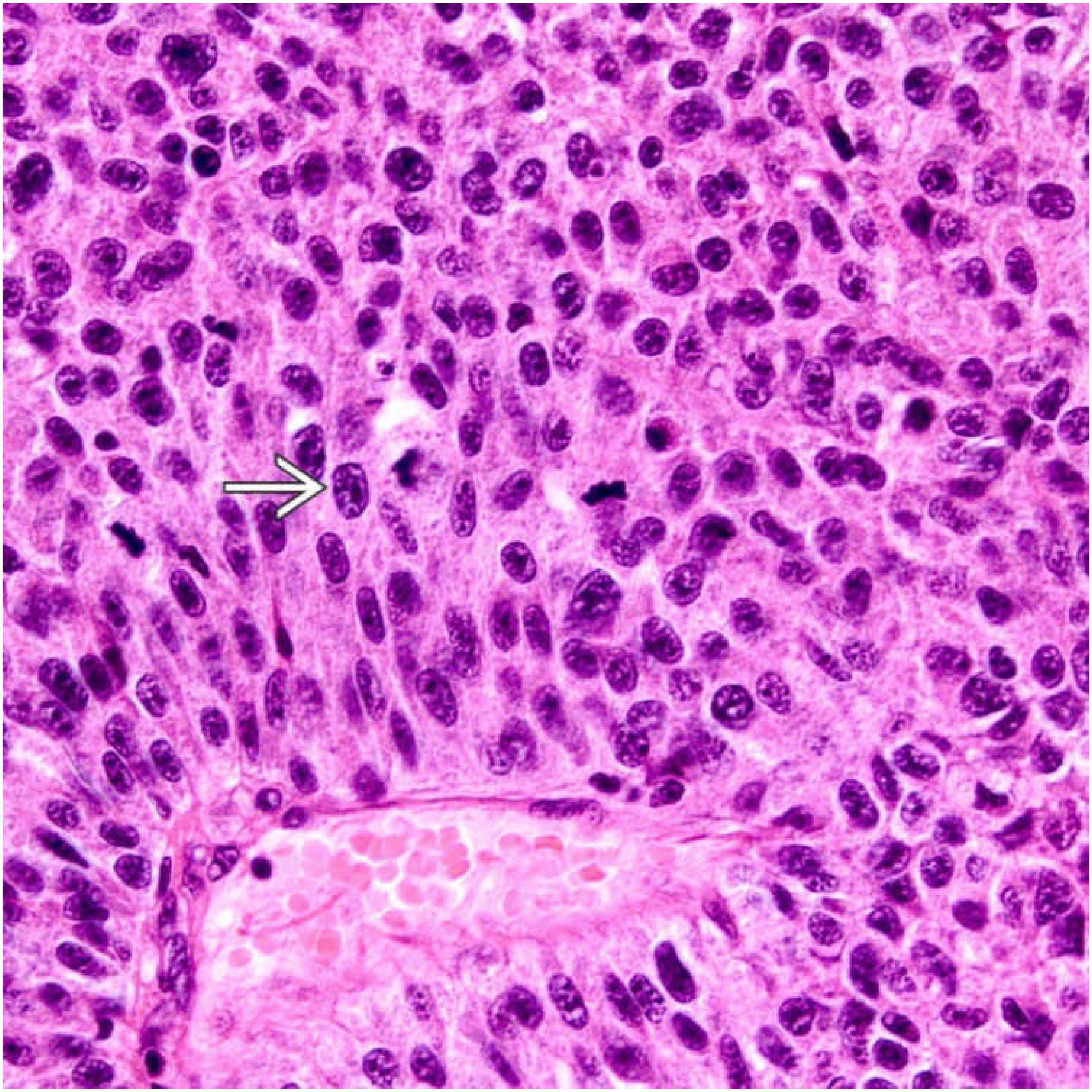


Solid Pseudopapillary Tumor
Solid pseudopapillary tumor is shown closely mimicking a neuroendocrine tumor; however, oval nuclei are seldom seen in pancreatic neuroendocrine tumors. Immunohistochemical distinction between these tumors is usually straightforward.



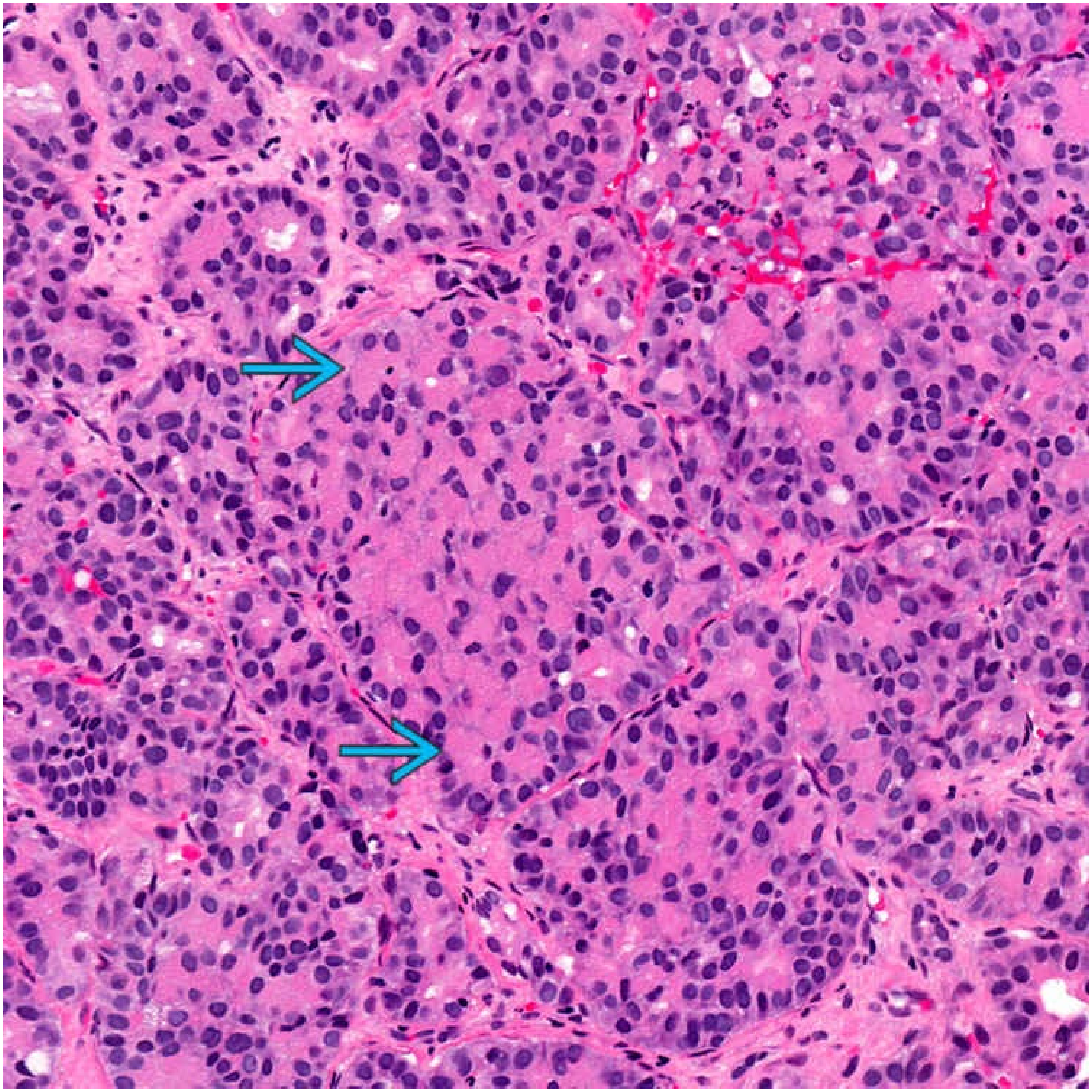
Acinar Architecture

Predominantly glandular/acinar pattern of growth may mimic acinar cell carcinoma. Large prominent nucleoli, brisk mitoses, and expression of trypsin supports acinar cell carcinoma.

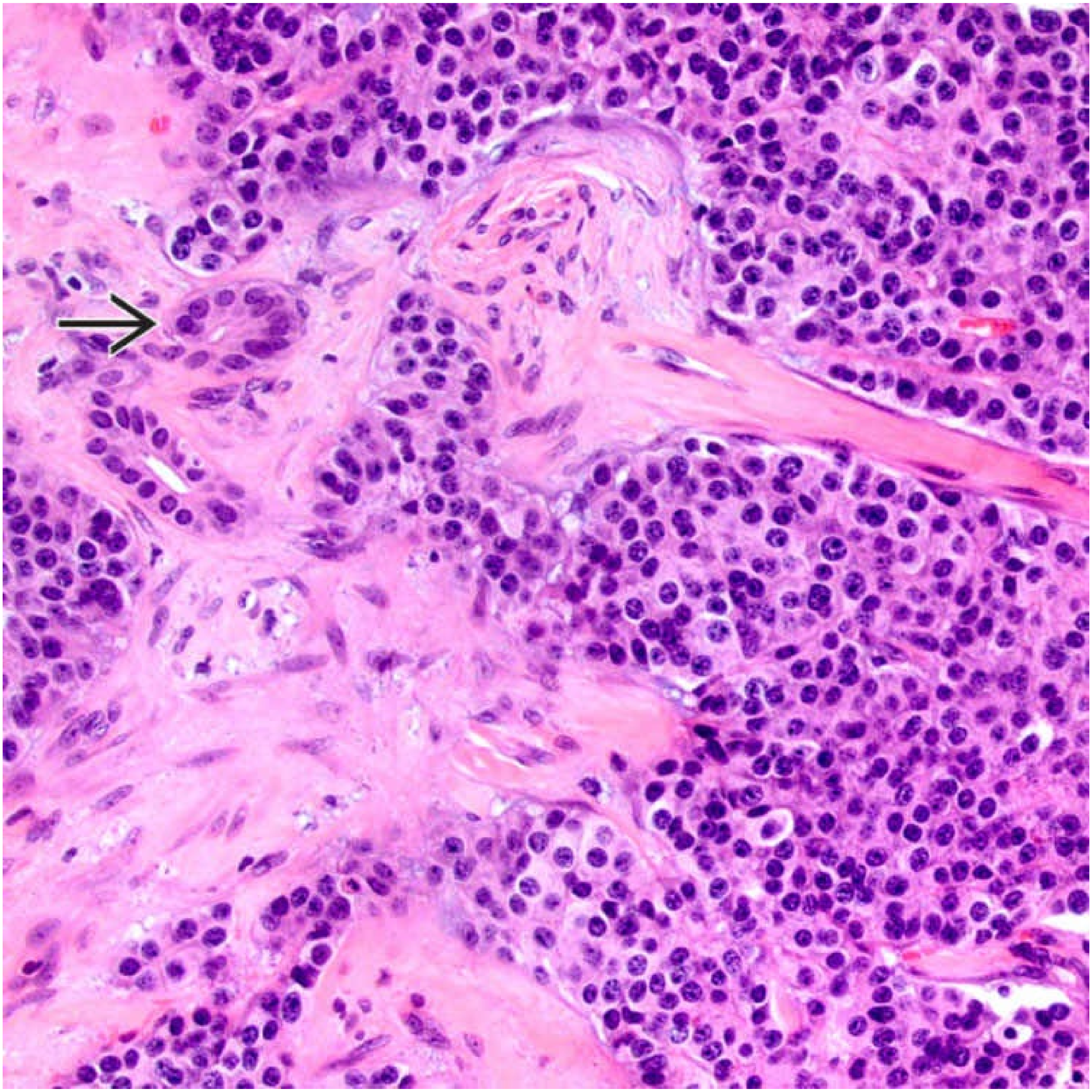


Acinar Cell Carcinoma

Acinar cell carcinoma with a solid growth pattern may mimic a pancreatic endocrine tumor. The large and prominent nucleoli ⇒ would favor acinar cell carcinoma; however, immunohistochemical analysis is required to make this distinction.



Metastatic Acinar Cell Carcinoma
Liver metastasis from pancreatic acinar cell carcinoma can mimic neuroendocrine tumors and can show patchy staining for neuroendocrine markers. Presence of cytoplasmic eosinophilic granules → and immunohistochemistry for trypsin help to confirm the diagnosis.



Entrapped Ducts
Pancreatic neuroendocrine tumor with entrapped ducts → is shown. This does not indicate a mixed ductal-endocrine tumor.

SELECTED REFERENCES

1. Agaimy, A, et al. ISL1 expression is not restricted to pancreatic well-differentiated neuroendocrine neoplasms, but is also commonly found in well and poorly differentiated neuroendocrine neoplasms of extrapancreatic origin. *Mod Pathol*. 2013; 26(7):995–1003.
2. McCall, CM, et al. Grading of well-differentiated pancreatic neuroendocrine tumors is improved by the inclusion of both Ki67 proliferative index and mitotic rate. *Am J Surg Pathol*. 2013; 37(11):1671–1677.
3. Hermann, G, et al. Hormonally defined pancreatic and duodenal neuroendocrine tumors differ in

their transcription factor signatures: expression of ISL1, PDX1, NGN3, and CDX2. *Virchows Arch*. 2011; 459(2):147–154.

4. Sangoi, AR, et al. PAX8 expression reliably distinguishes pancreatic well-differentiated neuroendocrine tumors from ileal and pulmonary well-differentiated neuroendocrine tumors and pancreatic acinar cell carcinoma. *Mod Pathol*. 2011; 24(3):412–424.
5. Klimstra, DS, et al. Pathology reporting of neuroendocrine tumors: application of the Delphic consensus process to the development of a minimum pathology data set. *Am J Surg Pathol*. 2010; 34(3):300–313.
6. Long, KB, et al. PAX8 Expression in well-differentiated pancreatic endocrine tumors: correlation with clinicopathologic features and comparison with gastrointestinal and pulmonary carcinoid tumors. *Am J Surg Pathol*. 2010; 34(5):723–729.
7. Srivastava, A, et al. Immunohistochemical staining for CDX-2, PDX-1, NESP-55, and TTF-1 can help distinguish gastrointestinal carcinoid tumors from pancreatic endocrine and pulmonary carcinoid tumors. *Am J Surg Pathol*. 2009; 33(4):626–632.
8. Chetty, R, et al. Membrane loss and aberrant nuclear localization of E-cadherin are consistent features of solid pseudopapillary tumour of the pancreas. An immunohistochemical study using two antibodies recognizing different domains of the E-cadherin molecule. *Histopathology*. 2008; 52(3):325–330.
9. Schmitt, AM, et al. Islet 1 (Isl1) expression is a reliable marker for pancreatic endocrine tumors and their metastases. *Am J Surg Pathol*. 2008; 32(3):420–425.
10. Nassar, H, et al. High-grade neuroendocrine carcinoma of the ampulla of vater: a clinicopathologic and immunohistochemical analysis of 14 cases. *Am J Surg Pathol*. 2005; 29(5):588–594.
11. Hochwald, SN, et al. Prognostic factors in pancreatic endocrine neoplasms: an analysis of 136 cases with a proposal for low-grade and intermediate-grade groups. *J Clin Oncol*. 2002; 20(11):2633–2642.
12. Zamboni, G, et al. Small-cell neuroendocrine carcinoma of the ampullary region. a clinicopathologic, immunohistochemical, and ultrastructural study of three cases. *Am J Surg Pathol*. 1990; 14(8):703–713.
13. Albores-Saavedra, J, et al. Unusual types of gallbladder carcinoma. a report of 16 cases. *Arch Pathol Lab Med*. 1981; 105(6):287–293.

Solid-Pseudopapillary Tumors

KEY FACTS

Terminology

- Solid-pseudopapillary neoplasm
- Low-grade malignant neoplasm of uncertain cellular differentiation

Etiology/Pathogenesis

- 90-100% harbor mutations in *CTNNB1* gene

Clinical Issues

- Occurs predominately in young females
- Presents with nonspecific symptoms related to intraabdominal mass
- Can be located in head, body, or tail of pancreas
- Indolent and nonaggressive behavior
- Metastasis in 10-15% of cases to liver, peritoneum, and lymph node
- > 80% are cured with surgical resection

Microscopic

- Well-demarcated, large mass
  - Solid, monomorphic sheets of polygonal cells
  - Delicate vessels surrounded by hyalinized or myxoid stroma
  - Characteristic degenerative change
  - Pseudopapillae formation
- Intracytoplasmic eosinophilic hyaline globules, PASD(+)
- Uniform round to oval nuclei with finely dispersed chromatin
- Neoplastic cells often have nuclear grooves

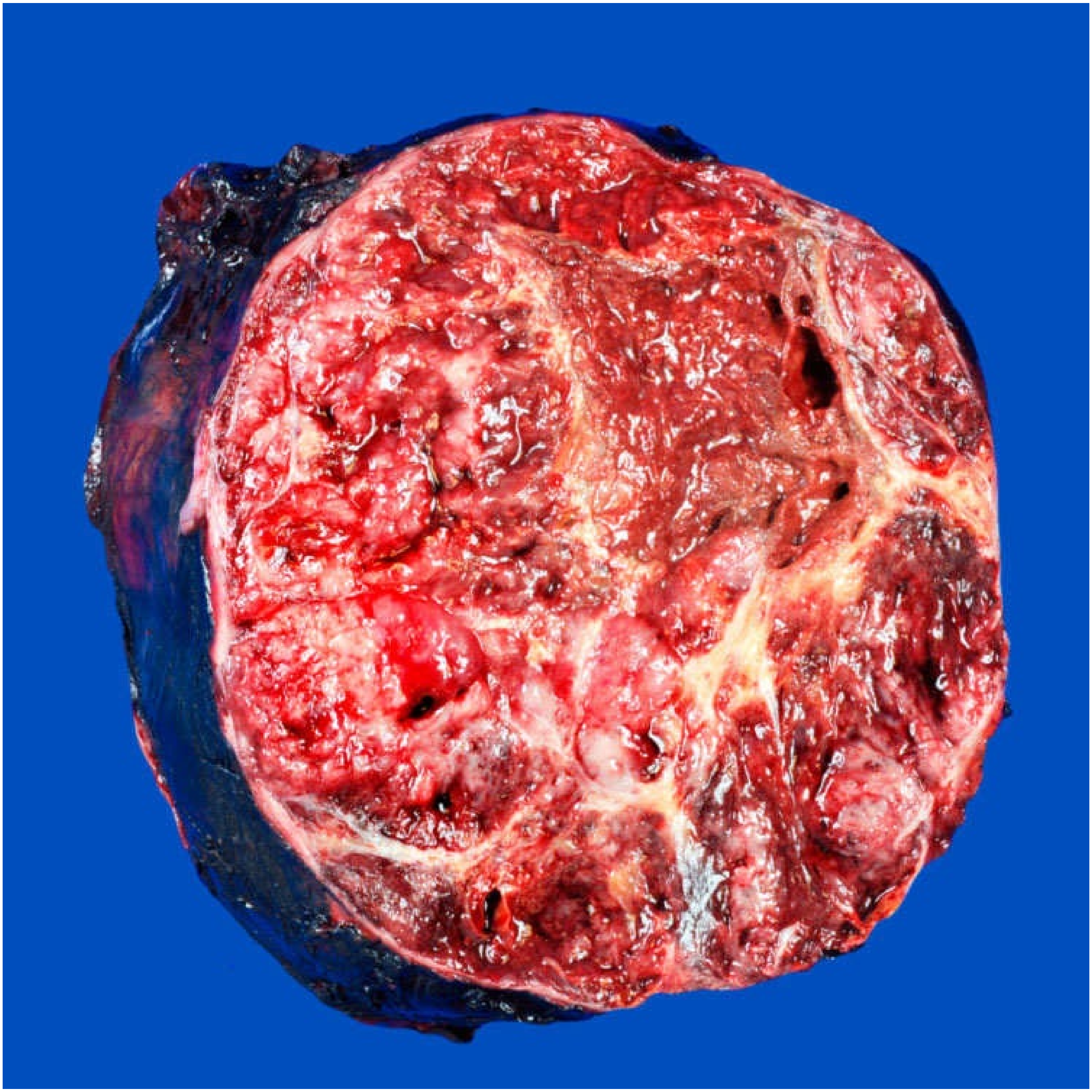
Ancillary Tests

- Immunohistochemistry: Nuclear β-catenin, cytoplasmic CD10, loss of membrane E-cadherin, nuclear

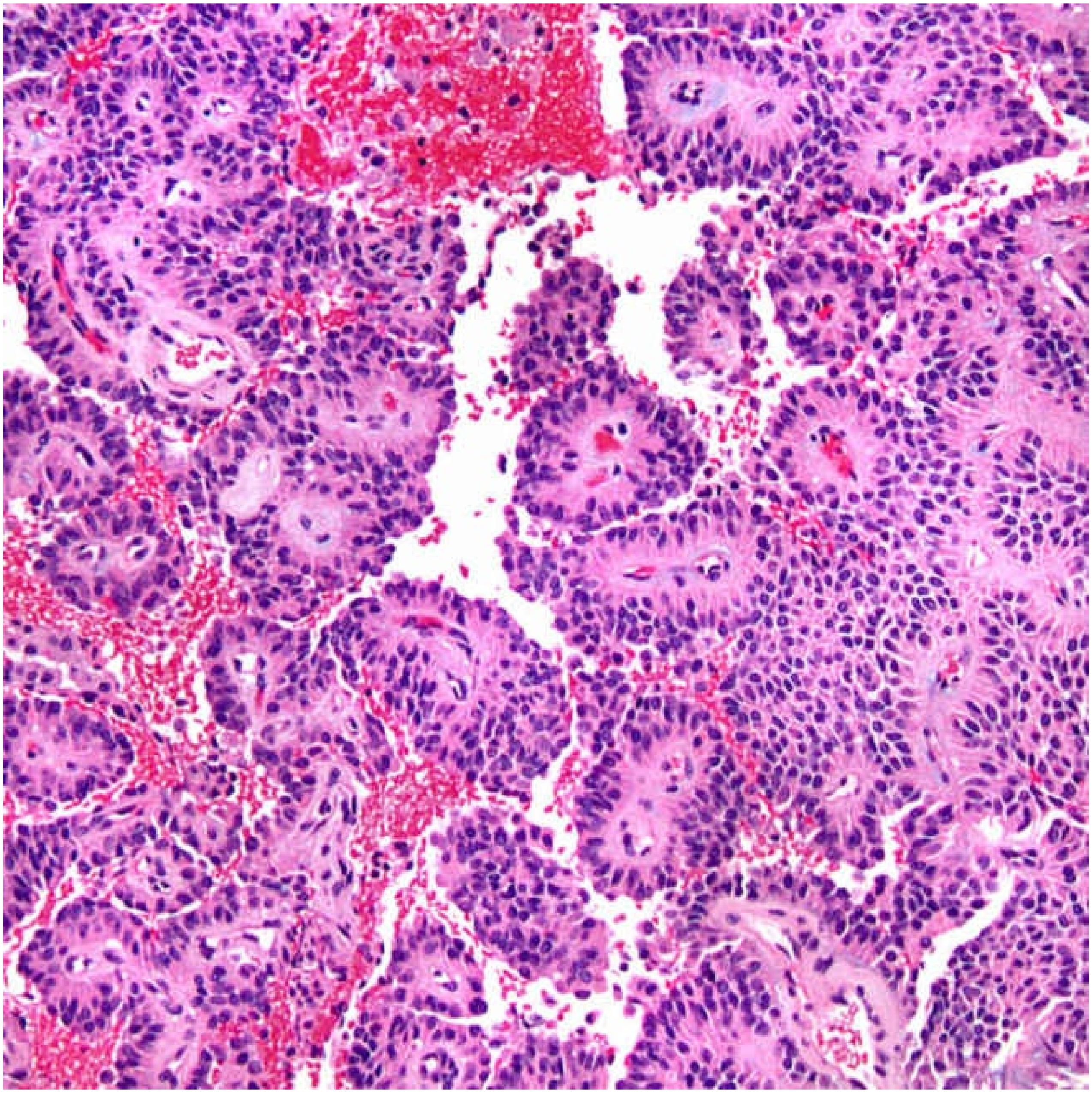
progesterone receptor

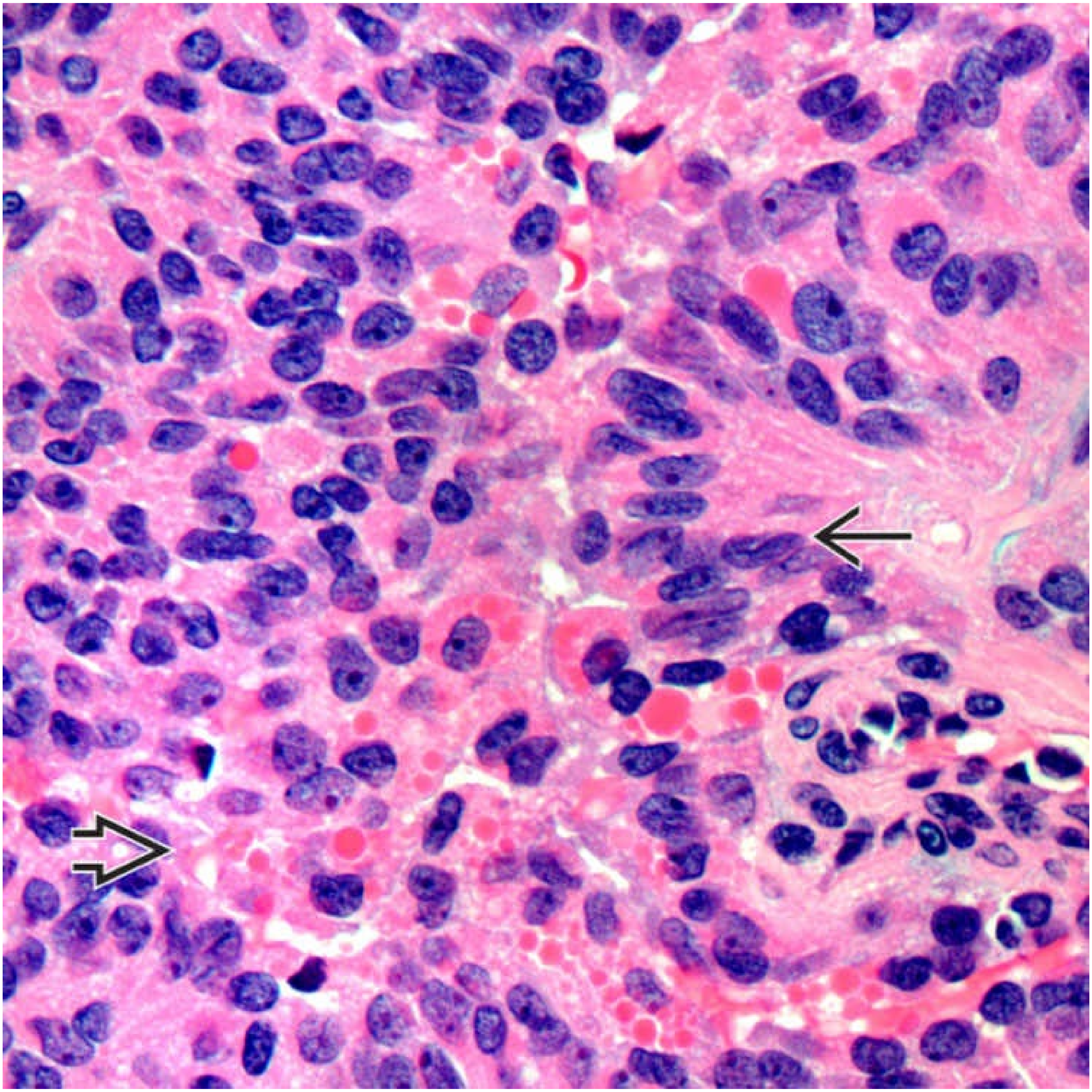
Top Differential Diagnoses

- Pancreatic neuroendocrine tumor



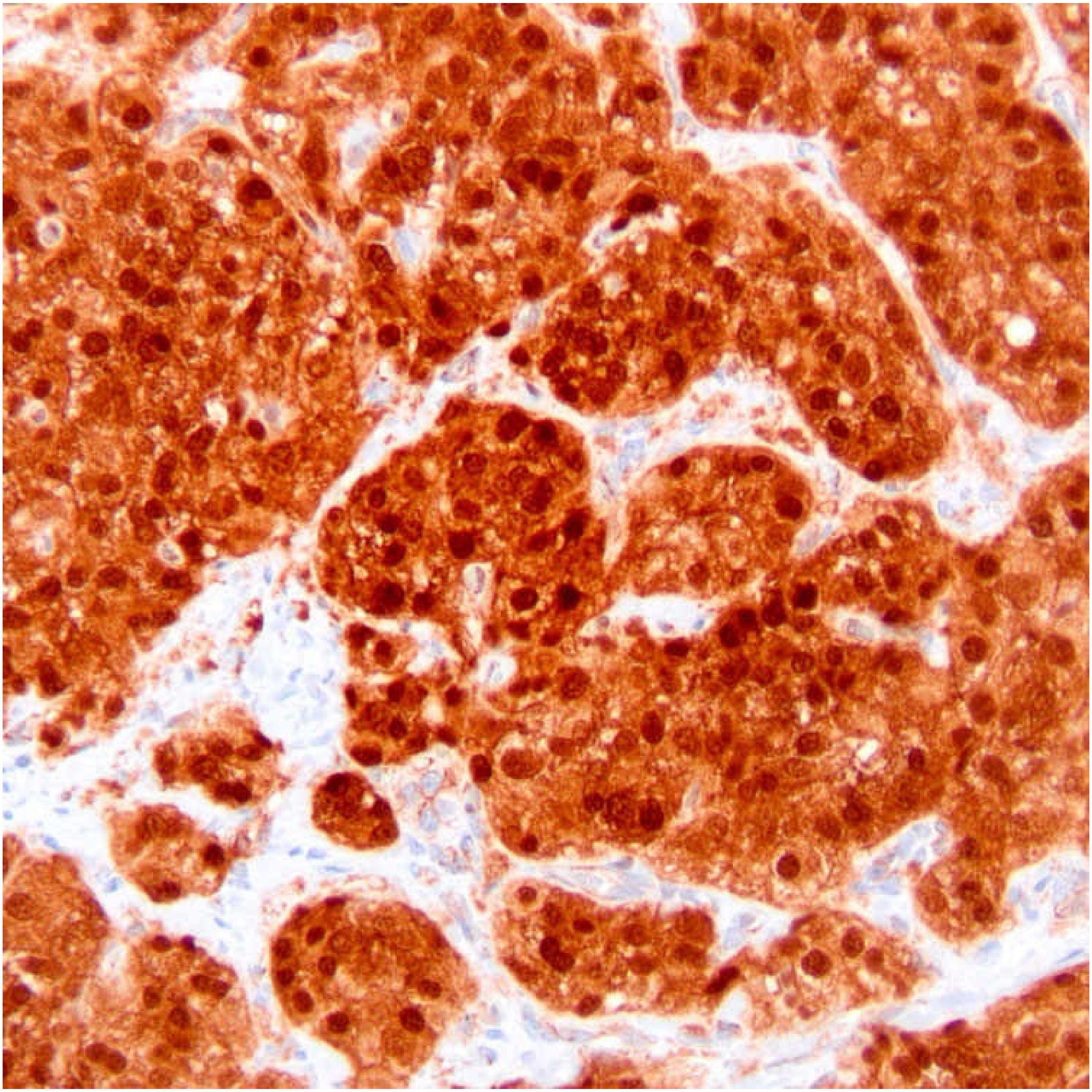
Gross Features
This well-demarcated tumor has a soft and friable solid surface with hemorrhagic areas.


Pseudopapillary Architecture
Solid sheets of tumor cells become dyscohesive and result in a characteristic pseudopapillary appearance with a central fibrovascular-like core surrounded by neoplastic cells.



Nuclear Grooves

Tumor cells have round to oval nuclei and sometimes exhibit longitudinal nuclear grooves →. These intra- and extracytoplasmic eosinophilic hyaline globules ⇨ stain positive for PASD and α-1-antitrypsin.



β-catenin Stain
Immunohistochemistry for β-catenin shows nuclear and cytoplasmic staining in > 90% of tumors.

TERMINOLOGY

Abbreviations

- Solid-pseudopapillary tumor (SPT)
- Solid-pseudopapillary neoplasm (SPN)

Synonyms

- Solid and papillary epithelial neoplasm

- Solid cystic tumor
- Papillary and cystic neoplasm
- Frantz tumor

Definitions

- Low-grade malignant neoplasm of uncertain cellular differentiation
- Originally described in 1959

ETIOLOGY/PATHOGENESIS

Cellular Lineage

- Uncertain, electron microscopy shows evidence of epithelial differentiation

Molecular

- 90-100% harbor mutations in *CTNNB1* gene

CLINICAL ISSUES

Epidemiology

- Incidence
  - Uncommon (1-2% of all exocrine pancreatic tumors)
- Age
  - Most patients in 20s and 30s
    - Mean age: 25-35 years
    - Overall age range: 7-79 years
- Sex
  - Female predominance (M:F = 1:9-20)

Site

- Evenly distributed throughout pancreas

Presentation

- Nonspecific symptoms related to intraabdominal mass
  - Vague abdominal pain, weight loss, anorexia
- May have palpable abdominal mass
- Up to 1/3 of cases discovered incidentally
- Complications: Rupture, hemoperitoneum

Laboratory Tests

- Serum oncomarkers, laboratory tests usually normal

Natural History

- Most are indolent, slow-growing, and nonaggressive
  - May directly invade stomach, duodenum, spleen
  - Metastasis
    - 10-15% of cases
    - Liver, peritoneum, lymph nodes
      - Peritoneal metastases more common in patients with trauma, rupture, or drainage of neoplasm
- Rare, clinically aggressive variant

Treatment

- Surgical resection is treatment of choice
- Can recur if incompletely resected

Prognosis

- Excellent
  - > 80% cured with surgical resection
  - 10-15% of cases have metastases or recurrence
  - Even patients with metastases have favorable long-term survival
- No proven morphologic predictors of outcome

IMAGING

General Features

- Radiographic features reflect variable gross findings
  - Well-circumscribed neoplasm with solid and cystic components
  - Calcifications in ~ 30%

Ultrasonographic Findings

- Well-demarcated, heterogeneous mass
- Variable echo texture

CT Findings

- Heterogeneous, well-circumscribed mass
- Areas with differing attenuation
- Variably present fluid/debris levels
- Pancreatic and bile ducts not dilated

MACROSCOPIC

General Features

- Large solitary mass
  - Rarely multiple
  - Well circumscribed, can be encapsulated
  - Solid to cystic, usually mixed
  - – Cystic areas often contain friable, necrotic material
  - – Minority of tumors are almost completely solid or completely cystic
- White-gray to yellow cut surface
- Evenly distributed throughout pancreas

Size

- Range: 1.5-25 cm
- Mean diameter: 9-10 cm

MICROSCOPIC

Histologic Features

- Solid monomorphic sheets of polygonal cells
  - Admixed delicate vessels surrounded by hyalinized or myxoid stroma
  - True glandular lumina not present
- Infrequent mitotic figures
- Perineural and true vascular invasion are quite rare
- Marked degenerative changes
  - Pseudopapillae formation
  - Foamy macrophages
  - Cholesterol clefts
  - Hemorrhage
  - Lipofuscin or melanin pigment
  - Calcification/ossification
  - Areas of infarction
    - – Although true tumor necrosis is rare
- Interface with normal pancreas
  - Infiltration of adjacent parenchyma is common
  - "Blood lakes" common at periphery of neoplasm
  - May have fibrous capsule

Cytologic Features

- Nuclei can be oriented away from vessels with zone of cytoplasm separating nuclei from capillaries
  - Uniform and round to oval with finely dispersed nuclear chromatin

- Often with longitudinal nuclear grooves
- Moderate amount of eosinophilic cytoplasm but can be clear with vacuoles
- Intracytoplasmic eosinophilic hyaline globules

ANCILLARY TESTS

Histochemistry

- PASD(+) intracytoplasmic eosinophilic hyaline globules

Immunohistochemistry

- Most useful antibodies
  - Cytoplasmic or perinuclear staining with CD10
  - Nuclear staining with β-catenin
  - Nuclear staining with progesterone receptor, estrogen receptor negative
  - E-cadherin: Loss of membrane staining (using antibodies to extracellular domain)
  - Synaptophysin can be positive, chromogranin is negative in most cases
  - Overexpression of transcription factor for immunoglobulin heavy chain enhancer 3 (TFE3) has been reported in recent studies, but presence of TFE3-associated translocation is not known
  - Pankeratin is variably positive

Molecular Genetics

- Missense mutations in exon 3 of *CTNNB1* in nearly all cases
- Prevents degradation of β-catenin protein and lead to its nuclear translocation
- No EWS-FLI1 translocation despite FLI-1 staining on immunohistochemistry

DIFFERENTIAL DIAGNOSIS

Pseudocyst

- No epithelial lining; entire cyst should be submitted
- More common in men
- History of pancreatitis, elevated amylase
- High levels of amylase in cyst fluid

Pancreatic Neuroendocrine Tumor

- Salt and pepper chromatin (low-grade tumors)
- Positive for keratin, synaptophysin, and chromogranin
- Membrane staining with β-catenin and E-cadherin
- CD10 and progesterone receptor can be positive

Acinar Cell Carcinoma

- Typically solid neoplasm
  - Cytologically different
  - Cohesive cells
  - Granular cytoplasm
  - More nuclear pleomorphism and mitoses
  - Prominent nucleoli
- Lumina can be present
- Keratin, trypsin &/or chymotrypsin, Bcl-6 (+)
- No nuclear β-catenin; can be positive for α-1-antitrypsin

Serous Neoplasms

- Lined by single layer of clear cells
- PAS positive, diastase sensitive due to glycogen content
- Keratin positive; no nuclear β-catenin

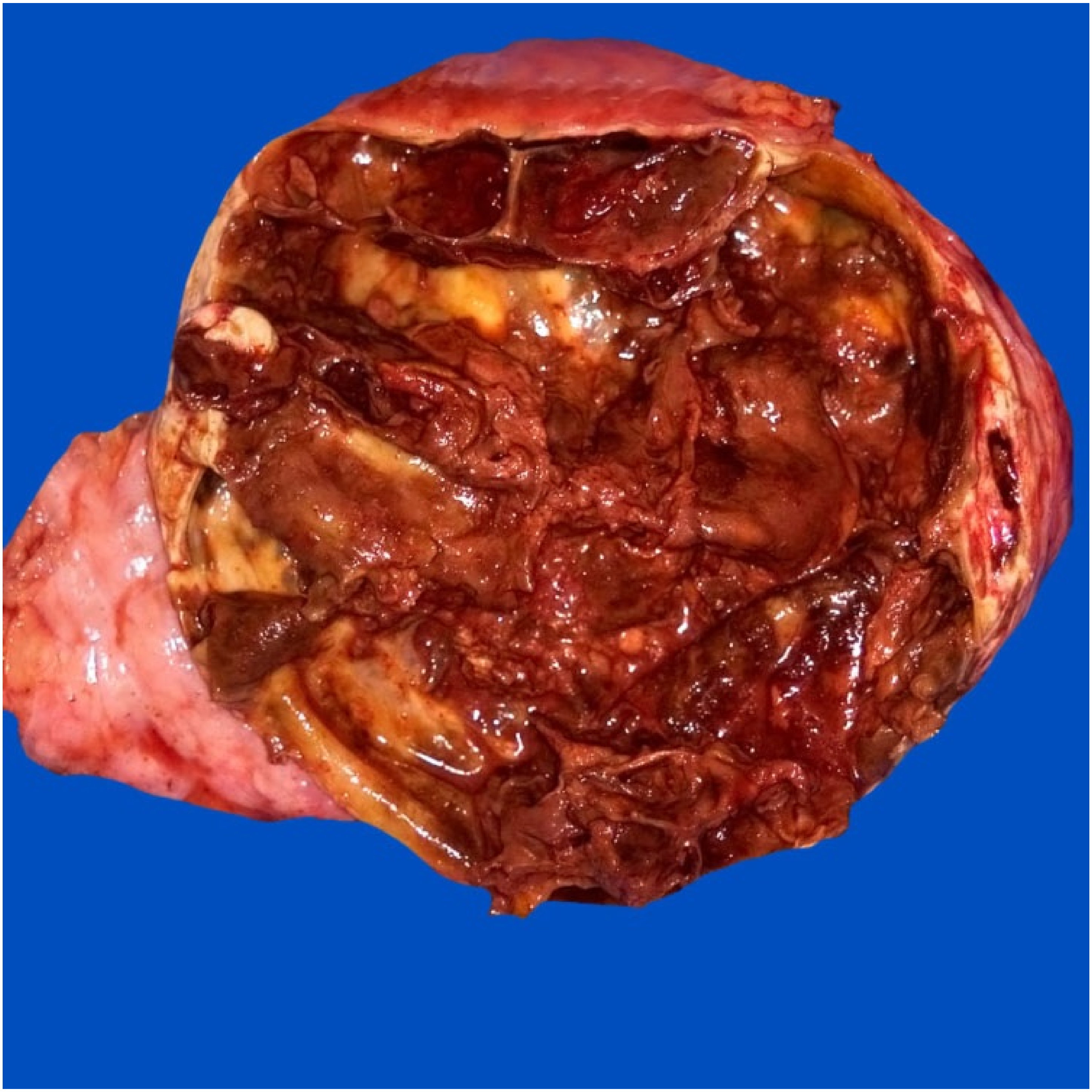
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

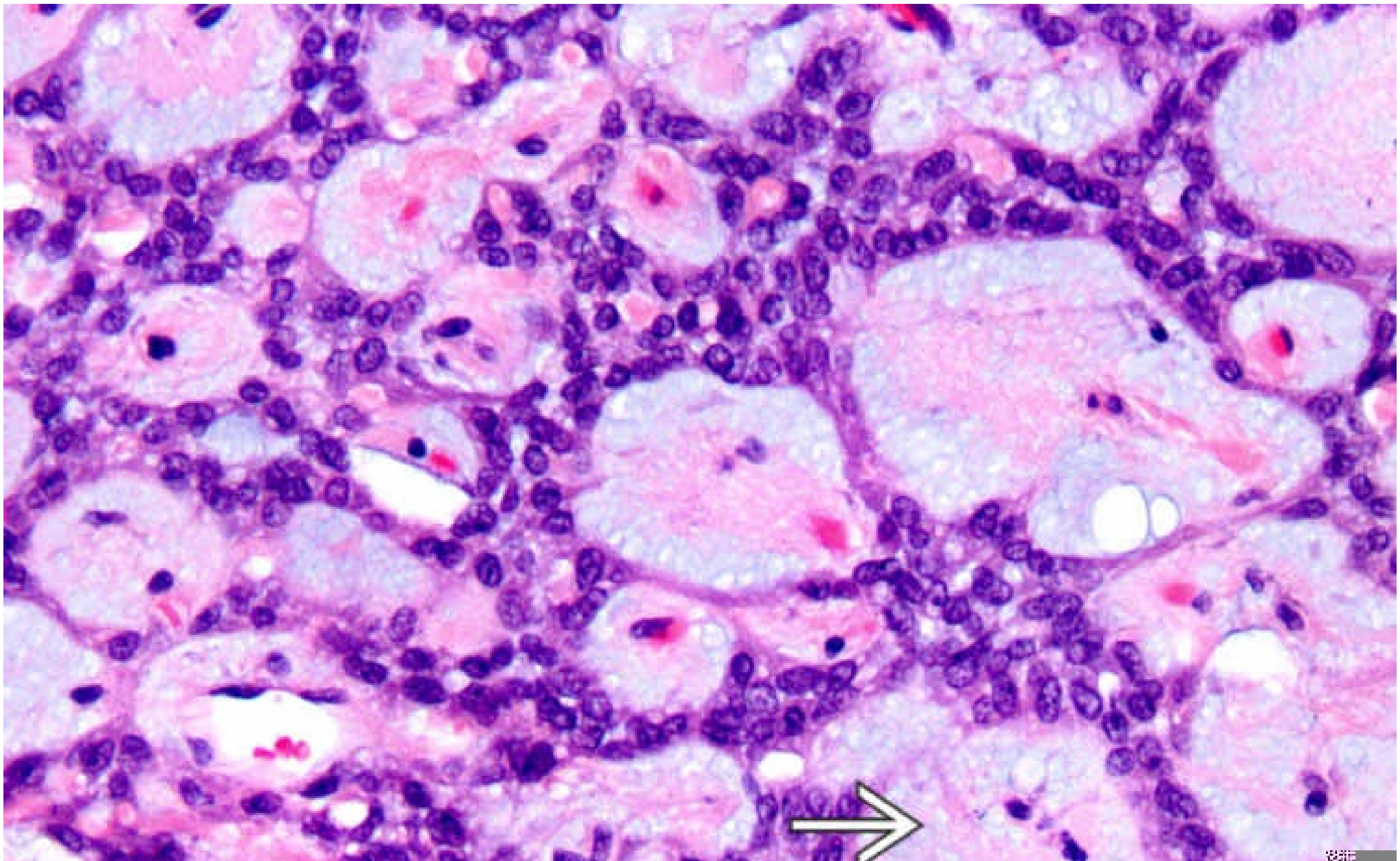
- Typically in young women
- Solid and cystic gross appearance

Pathologic Interpretation Pearls

- Nuclear staining for β-catenin
- Nuclear grooves, pseudopapillae are characteristic



Gross Features
The tumor can present as a well-demarcated, hemorrhagic cystic mass mimicking a pseudocyst.

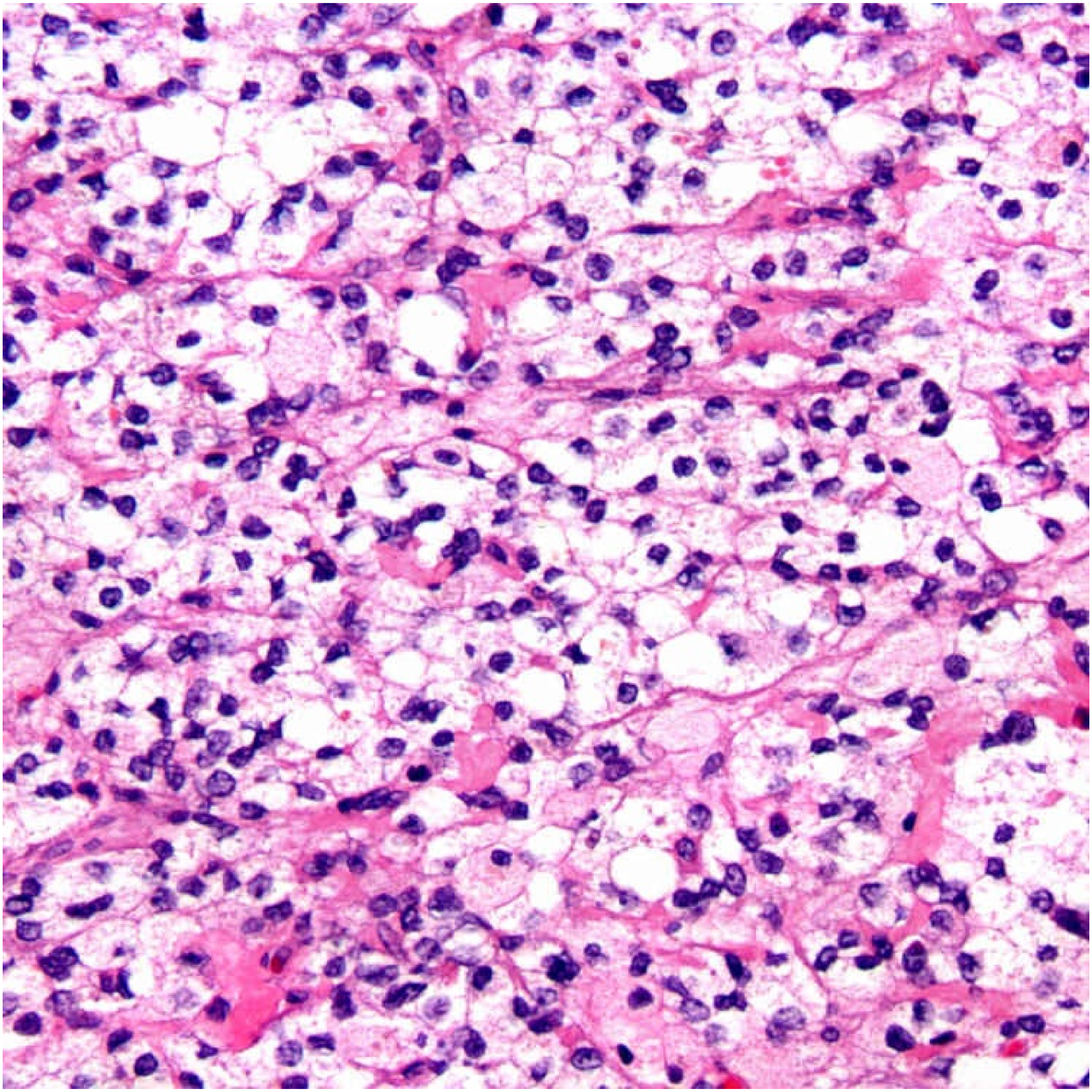


Myxoid Stroma

The delicate vessels can have myxoid stroma or may be hyalinized.

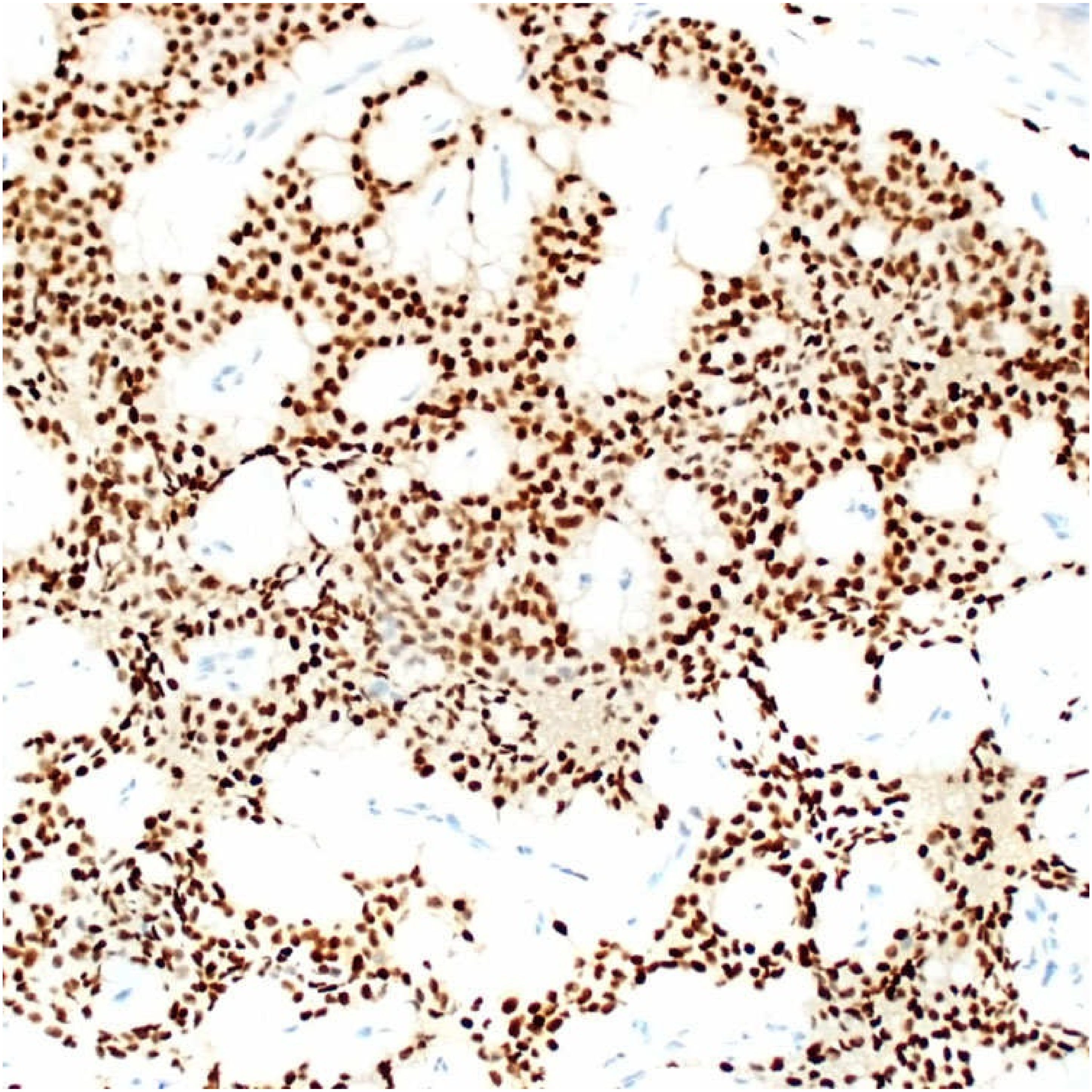
Cytologic Features

The sheets of tumor cells have overlapping, round to oval nuclei that are oriented away from the vessels → with a rim of cytoplasm toward the capillary.

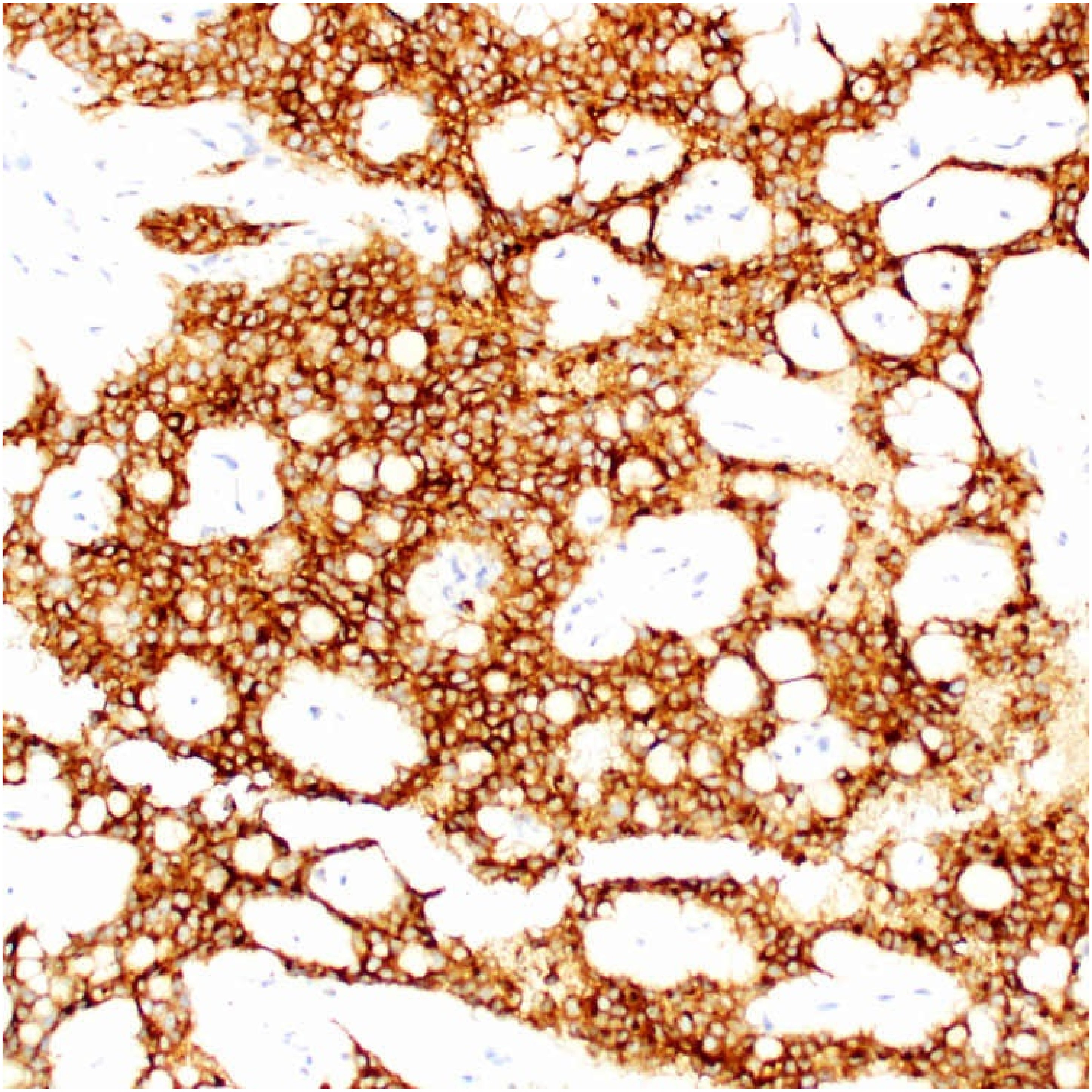


Clear Cell Change

Typically the neoplastic cells are polygonal with eosinophilic cytoplasm, but these tumors can also have clear cytoplasm or, rarely, be composed of monomorphic spindle cells.



Progesterone Receptor
Immunohistochemistry for progesterone receptor shows nuclear staining in nearly 80% of solid-pseudopapillary tumors. Staining for estrogen receptor is generally negative.



CD10
Immunohistochemistry for CD10 shows cytoplasmic staining in solid-pseudopapillary tumors in nearly all the cases. Perinuclear staining may be seen in some instances.

SELECTED REFERENCES

1. Uppin, SG, et al. Solid-pseudopapillary neoplasm of the pancreas: a clinicopathological and immunohistochemical study of 33 cases from a single institution in Southern India. *Indian J Pathol Microbiol*. 2015; 58(2):163–169.
2. Li, L, et al. Immunohistochemical evaluation of solid pseudopapillary tumors of the pancreas: the expression pattern of CD99 is highly unique. *Cancer Lett*. 2011; 310(1):9–14.
3. Nguyen, NQ, et al. Clinical and immunohistochemical features of 34 solid pseudopapillary tumors of the pancreas. *J Gastroenterol Hepatol*. 2011; 26(2):267–274.

4. Basturk, O, et al. Pancreatic cysts: pathologic classification, differential diagnosis, and clinical implications. *Arch Pathol Lab Med*. 2009; 133(3):423–438.
5. Comper, F, et al. Expression pattern of claudins 5 and 7 distinguishes solid-pseudopapillary from pancreatoblastoma, acinar cell and endocrine tumors of the pancreas. *Am J Surg Pathol*. 2009; 33(5):768–774.
6. Adsay, NV. Cystic neoplasia of the pancreas: pathology and biology. *J Gastrointest Surg*. 2008; 12(3):401–404.
7. Klimstra, DS. Nonductal neoplasms of the pancreas. *Mod Pathol*. 2007; 20(Suppl 1):S94–112.
8. Tang, WW, et al. Loss of cell-adhesion molecule complexes in solid pseudopapillary tumor of pancreas. *Mod Pathol*. 2007; 20(5):509–513.
9. Tang, LH, et al. Clinically aggressive solid pseudopapillary tumors of the pancreas: a report of two cases with components of undifferentiated carcinoma and a comparative clinicopathologic analysis of 34 conventional cases. *Am J Surg Pathol*. 2005; 29(4):512–519.
10. Kosmahl, M, et al. Cystic neoplasms of the pancreas and tumor-like lesions with cystic features: a review of 418 cases and a classification proposal. *Virchows Arch*. 2004; 445(2):168–178.
11. Abraham, SC, et al. Solid-pseudopapillary tumors of the pancreas are genetically distinct from pancreatic ductal adenocarcinomas and almost always harbor beta-catenin mutations. *Am J Pathol*. 2002; 160(4):1361–1369.
12. Notohara, K, et al. Solid-pseudopapillary tumor of the pancreas: immunohistochemical localization of neuroendocrine markers and CD10. *Am J Surg Pathol*. 2000; 24(10):1361–1371.

SECTION 6
TUMORS OF THE AMPULLA

OUTLINE

Ampullary Adenoma

KEY FACTS

Terminology

- Intestinal-type premalignant epithelial neoplastic lesion of ampulla of Vater

Clinical Issues

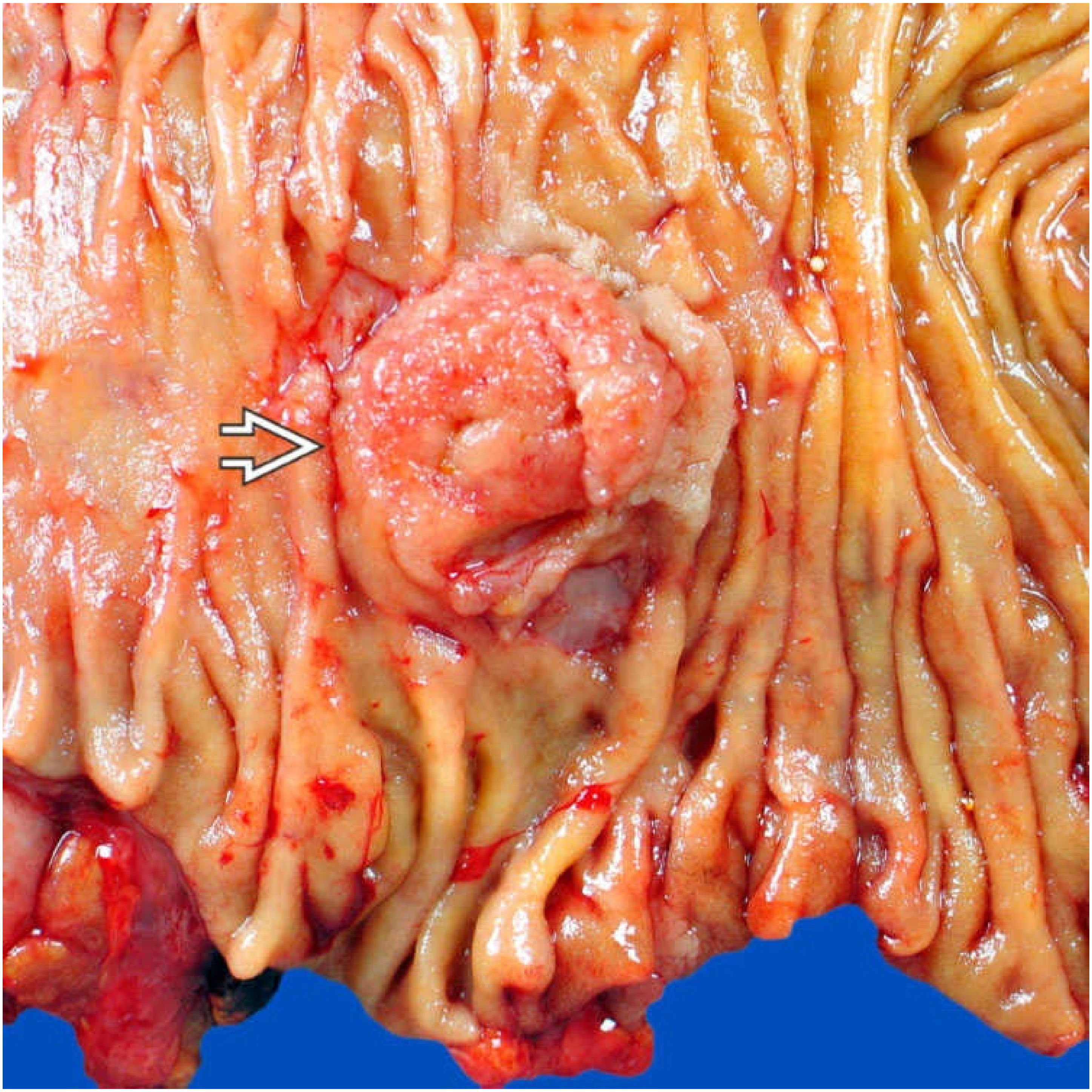
- 0.04-0.12% of individuals based on autopsy data
  - Most are sporadic
- Seen in 50-100% of patients with familial adenomatous polyposis and Gardner syndrome
  - Most common site of extracolonic polyps in syndromic patients
- Signs and symptoms of biliary or pancreatic obstruction
- Precursor of ampullary adenocarcinoma
  - 124x increased risk in syndromic patients
- Endoscopic findings
  - Soft polyp or plaque with regular margins
  - Prominence or mucosal thickening of papilla
  - Absence of ulceration or spontaneous bleeding
  - May extend into distal bile duct &/or pancreatic duct

Microscopic

- Tubular adenoma
  - Simple tubular glands resembling basal portions of normal intestinal crypts
  - < 25% of villous component
- Tubulovillous adenoma
  - > 25% of both tubular and villous components
- Villous adenoma
  - > 75% of villous component
  - Usually sessile
- Areas of high-grade dysplasia may be present

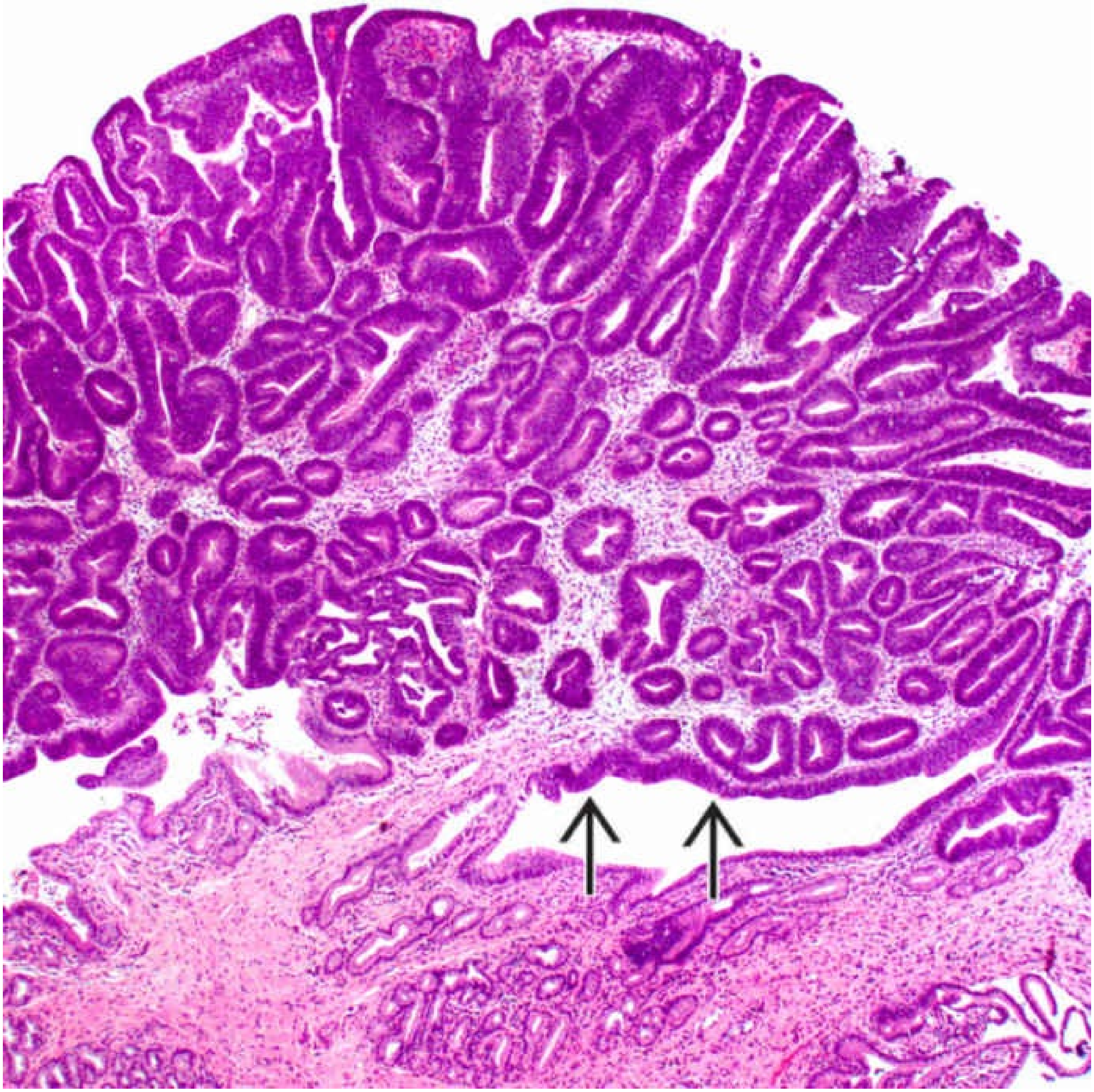
Top Differential Diagnoses

- Reactive epithelial atypia
  - Invasive ampullary adenocarcinoma
  - ○ Extension of adenomatous epithelium into underlying periampullary glands and ducts may mimic invasion
- Flat intraepithelial neoplasia (dysplasia)
- Noninvasive papillary neoplasm, pancreaticobiliary type



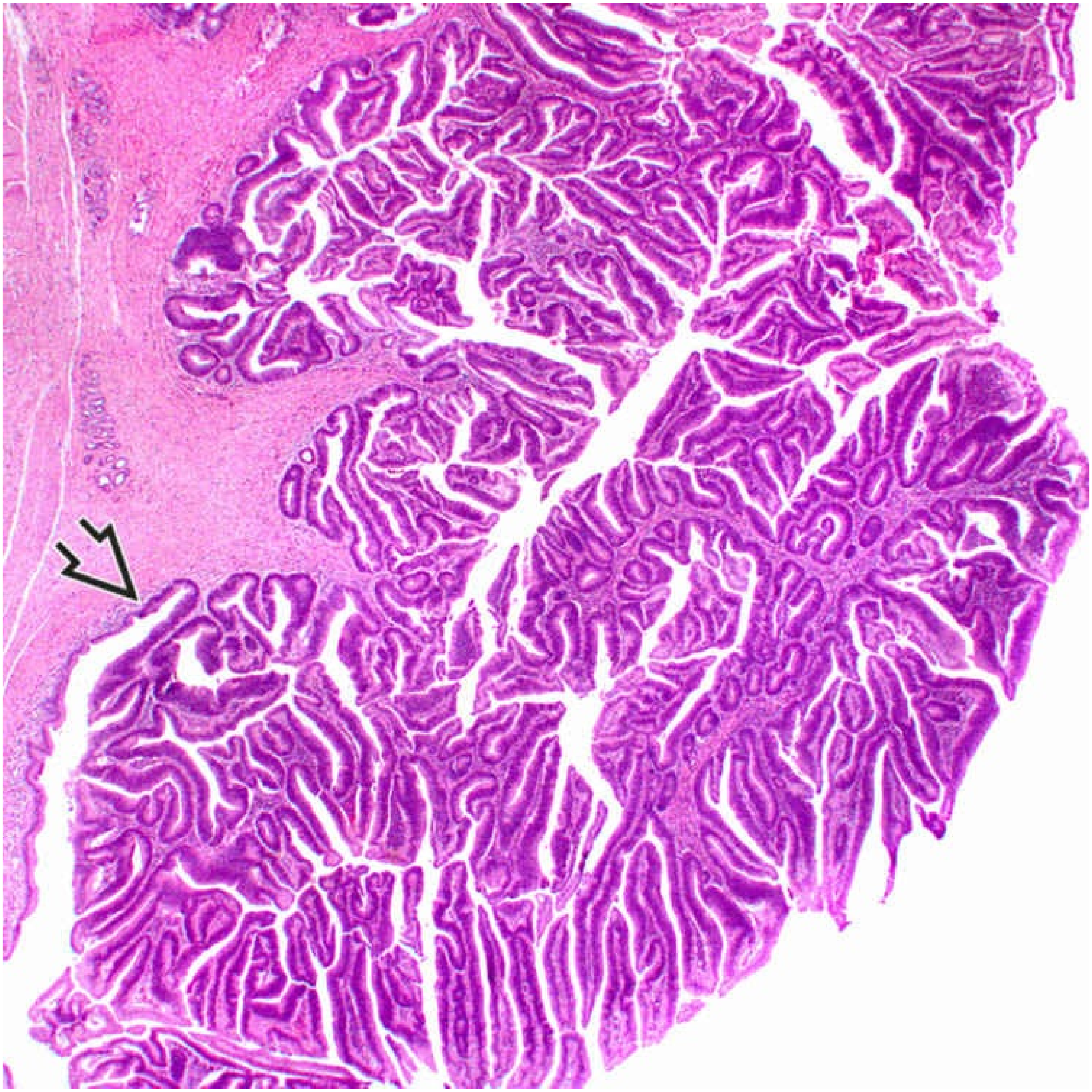
Gross Appearance

This surgically resected specimen shows a well-circumscribed mass lesion ⇨ occupying the ampulla of Vater that obstructs the common bile duct and pancreatic duct. Histologic examination shows tubulovillous adenoma with associated invasive adenocarcinoma.



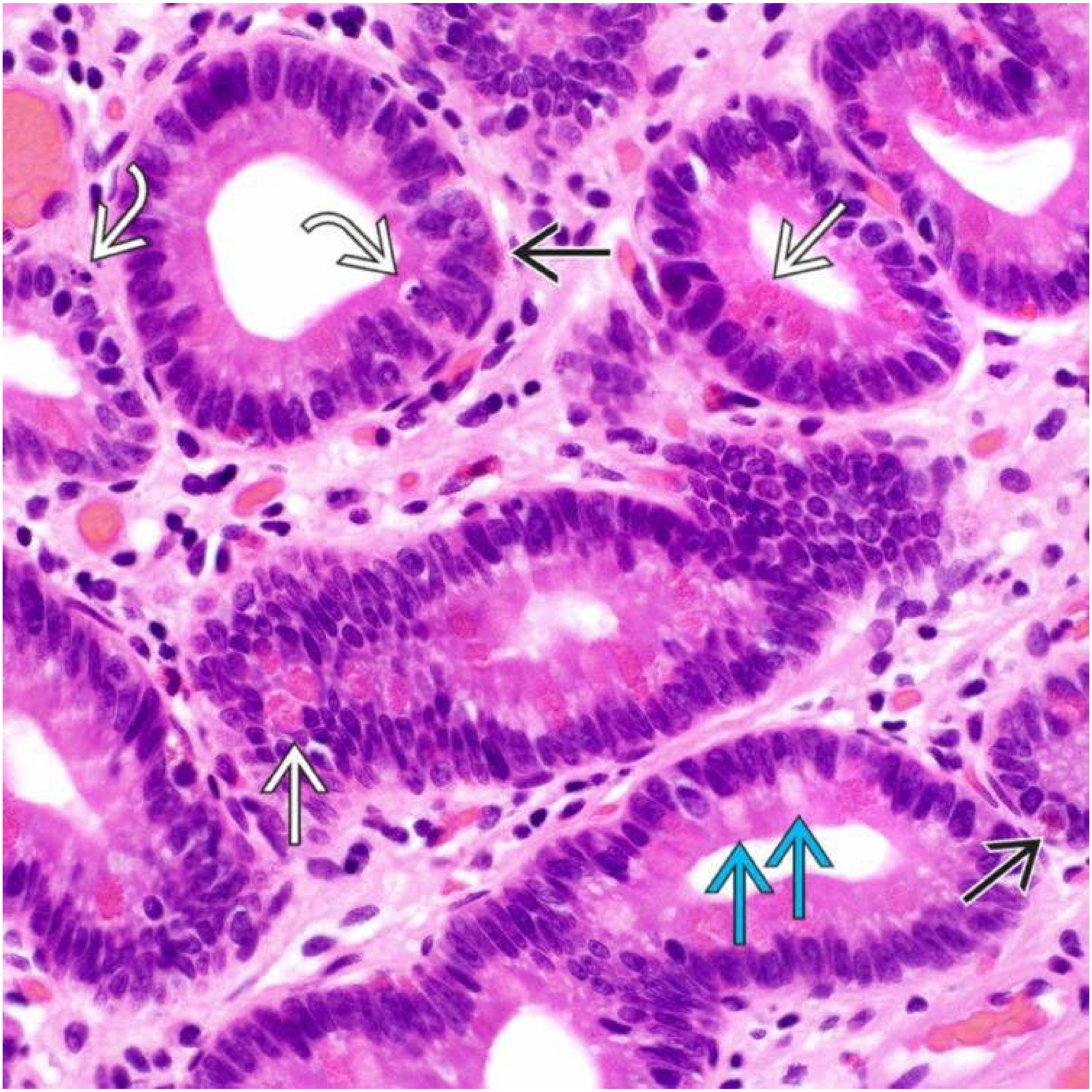
Tubular Adenoma

This polypoid ampullary lesion is a tubular adenoma. Note the extension of adenomatous epithelium into the underlying periampullary glands/ducts →.



Villous Adenoma

This ampullary lesion is a villous adenoma. It extends into the distal common bile duct and shows a continuum of the adenomatous epithelium with the nonneoplastic epithelium lining the bile duct ➪ .



Histologic Features
This ampullary adenoma shows predominantly basally located nuclei that are elongated, hyperchromatic, and pseudostratified. Numerous Paneth cells ⇨ are present in this case. Goblet cells → and endocrine cells → are also present. A few apoptotic bodies ↷ are seen.

TERMINOLOGY

Definitions

- Intestinal-type premalignant epithelial neoplastic lesion of ampulla of Vater

CLINICAL ISSUES

Epidemiology

- Incidence
  - 0.04-0.12% of individuals based on autopsy data
    - Most are sporadic
  - Seen in 50-100% of patients with familial adenomatous polyposis and Gardner syndrome
    - Most common site of extracolonic polyps in syndromic patients
- Age
  - Mean
    - 61 years (range: 33-81) for sporadic patients
    - 41 years for syndromic patients
- Sex
  - M:F = 1:2.6 in sporadic setting
  - No gender predominance in syndromic setting

Presentation

- Signs and symptoms of biliary or pancreatic obstruction
  - Painless jaundice seen in 50-75% of patients
  - Cholangitis &/or pancreatitis occasionally seen
  - Abdominal pain, nausea, vomiting, weight loss
- Asymptomatic, particularly in syndromic patients

Endoscopic Findings

- Soft polyp or plaque with regular margins
- Prominence or mucosal thickening of papilla
- Absence of ulceration or spontaneous bleeding
- Usually 1-3 cm in size in symptomatic cases
- Often also having multiple duodenal polyps in syndromic patients
- May extend into distal bile duct &/or pancreatic duct

Treatment

- Biopsy with close endoscopic surveillance
- Local excision including endoscopic or surgical ampullectomy
- Pancreatoduodenectomy for larger lesions, lesions containing carcinoma or with lymph node involvement

Prognosis

- Cured by complete excision
  - May recur after local excision in up to 33% patients
  - Precursor of ampullary adenocarcinoma

    - 124x increased risk in syndromic patients

Endoscopic Surveillance Following Local Excision

- Initial surveillance within 1-6 months
- Then every 3-12 months for next 2 years
- Less frequent intervals thereafter

IMAGING

Endoscopic Ultrasound

- Provides information regarding depth of lesion and locoregional lymph node status

Endoscopic Retrograde Cholangiopancreatography

- Provides information regarding extent of ingrowth of lesion into bile duct &/or pancreatic duct

MACROSCOPIC

General Features

- Polypoid or papillary growths

MICROSCOPIC

Histologic Features

- Tubular adenoma
    - Simple tubular glands resembling basal portions of normal intestinal crypts
    - < 25% of villous component
- Tubulovillous adenoma
    - > 25% of both tubular and villous components
- Villous adenoma
    - > 75% of villous component
    - Usually sessile
- Adenomatous epithelium
    - Predominantly basally located, elongated and hyperchromatic nuclei with pseudostratification
    - Amphophilic cytoplasm
    - May show increased apoptotic activity
    - Paneth, goblet, and endocrine cells are common
- Dysplasia
    - Low-grade dysplasia by definition
    - Areas of high-grade dysplasia may be present

– Complex glandular architecture such as cribriforming
– Marked nuclear atypia with rounded nuclei, prominent nucleoli, and loss of nuclear polarity

DIFFERENTIAL DIAGNOSIS

Reactive Epithelial Atypia

• Large nuclei with open chromatin and visible nucleoli
• Lack of nuclear pseudostratification
• Presence of inflammation
• History of procedure such as biliary stent placement

Invasive Ampullary Adenocarcinoma

• Extension of adenomatous epithelium into underlying periampullary glands and ducts may mimic invasion

Invasive Pancreaticobiliary Carcinoma

• Colonization of mucosal basement membrane by underlying carcinoma can mimic adenoma

Flat Intraepithelial Neoplasia (Dysplasia)

• Lack of polypoid lesion on endoscopy

Noninvasive Papillary Neoplasm, Pancreaticobiliary Type

• More prominent and complex papillary structure
• Closely resembling intraductal papillary neoplasms of pancreas and bile duct
• No Paneth cells

Invasive Pancreaticobiliary Adenocarcinoma

• Can mimic adenoma if invading ampulla with colonization of ampullary mucosa

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

• Degree of dysplasia may vary in different areas within 1 tumor, and invasive carcinoma, if present, may be focal

SELECTED REFERENCES

1. Espinel, J, et al. Endoscopic management of adenomatous ampullary lesions. *World J Methodol*. 2015; 5(3):127–135.
2. Moon, JH, et al. Current status of endoscopic papillectomy for ampullary tumors. *Gut Liver*. 2014; 8(6):598–604.
3. Chini, P, et al. Diagnosis and management of ampullary adenoma: The expanding role of endoscopy. *World J Gastrointest Endosc*. 2011; 3(12):241–247.

SECTION 7

SPECIMEN HANDLING, WHIPPLE

OUTLINE

Ampullary Adenocarcinoma and Variants

KEY FACTS

Terminology

- Malignant epithelial neoplasm originates in ampulla of Vater

Etiology/Pathogenesis

- Histogenesis
  - Intraampullary: Arise in ampulla (lined by pancreatobiliary epithelium)
  - Periampullary: Arise in duodenal surface of papilla (lined by intestinal epithelium)

Clinical Issues

- 5-year overall survival rate: 40%
  - Determined by histologic type, grade, stage, coexisting adenoma

Microscopic

- 2 main histologic types
  - Intestinal-type adenocarcinoma
    – Most common (50-80%)
    – Similar to adenocarcinoma of colon and small bowel
  - Pancreatobiliary-type adenocarcinoma
    – 2nd most common (15-20%)
    – Similar to pancreatic ductal or bile duct adenocarcinoma

Ancillary Tests

- Intestinal type
  - CK20, CDX-2, or MUC2 (+), MUC1(-)
  - CK20, CDX-2, and MUC2 (+), irrespective of MUC1

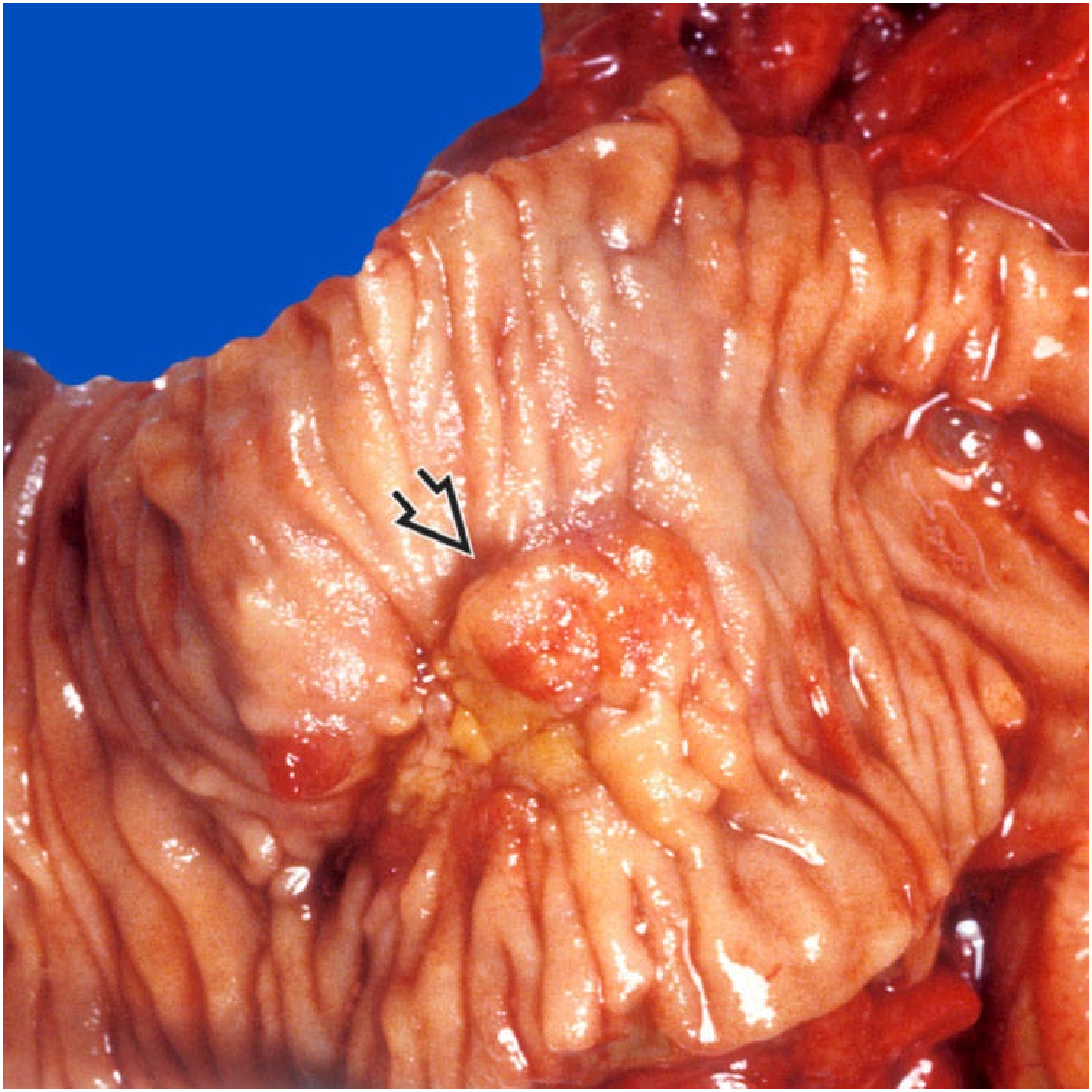
- Pancreatobiliary type
    - MUC1(+), CDX-2 and MUC2 (-)

Top Differential Diagnoses

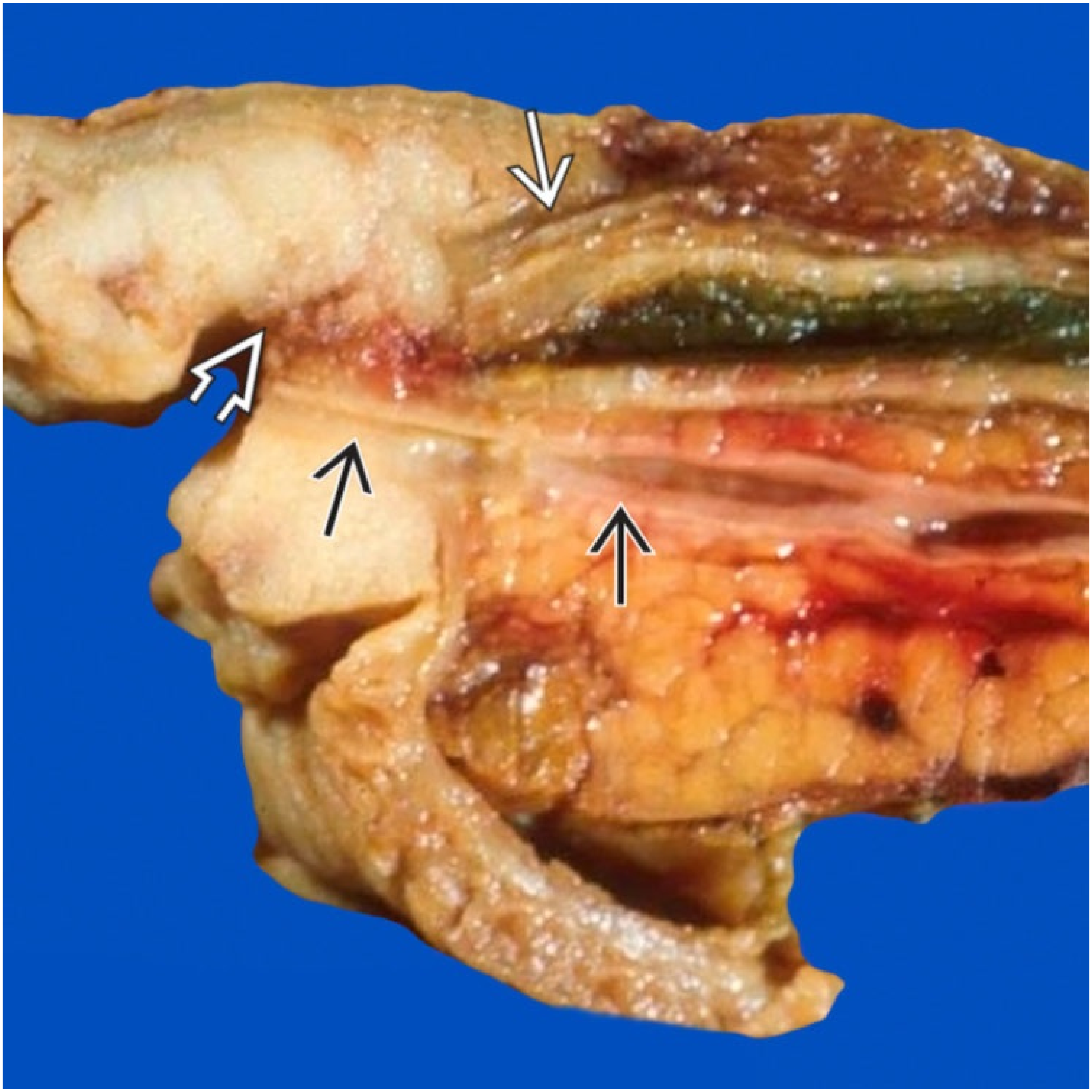
- Adenocarcinomas of pancreas, distal common bile duct, and duodenum

Diagnostic Checklist

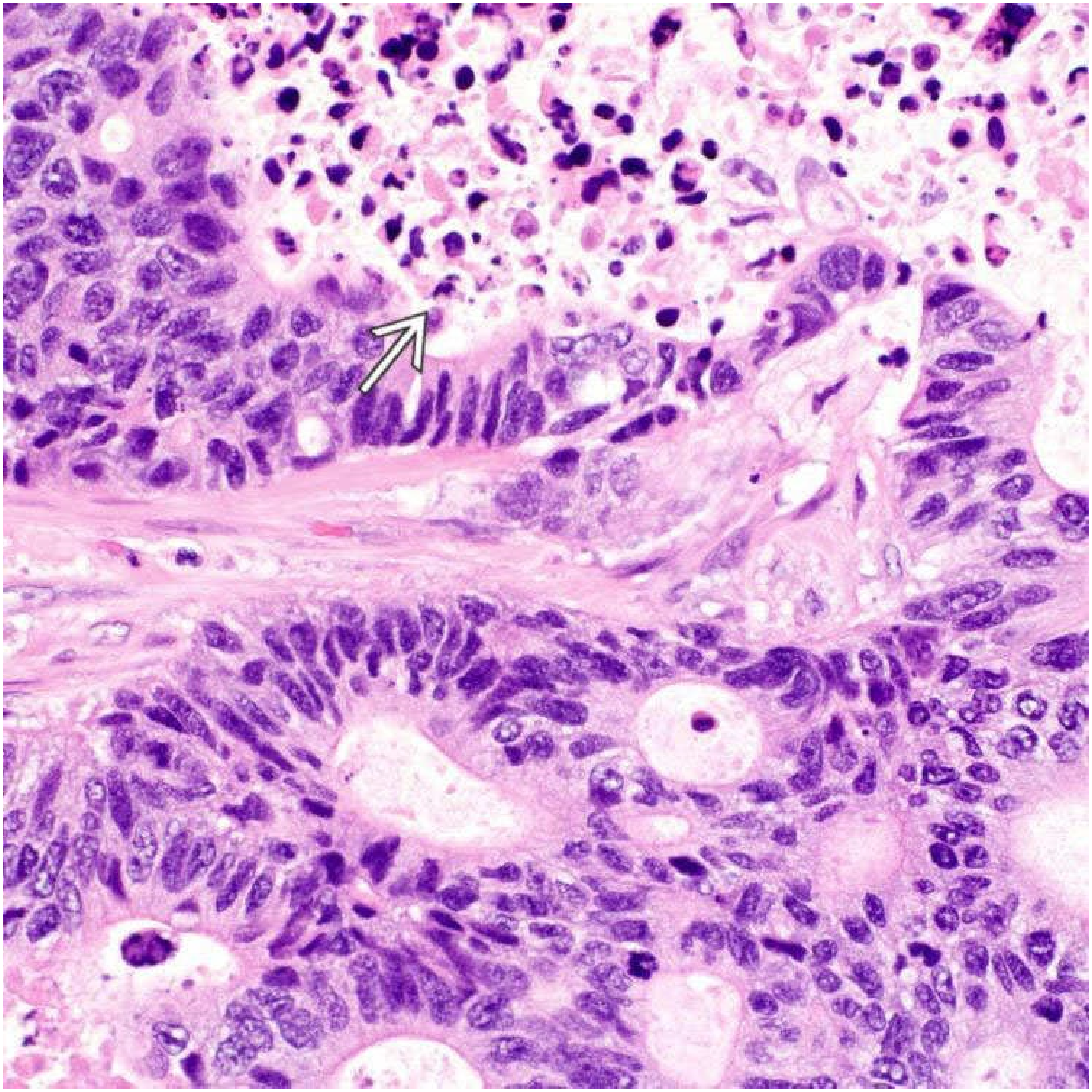
- Important to distinguish intestinal type from pancreatobiliary type because of more favorable prognosis



Ampullary Mass
From the luminal aspect of this resection specimen, the ampulla is replaced by an exophytic, ulcerated mass ⇨ involving the papilla and periampullary duodenal mucosa. Histologic examination confirms the diagnosis of ampullary adenocarcinoma.

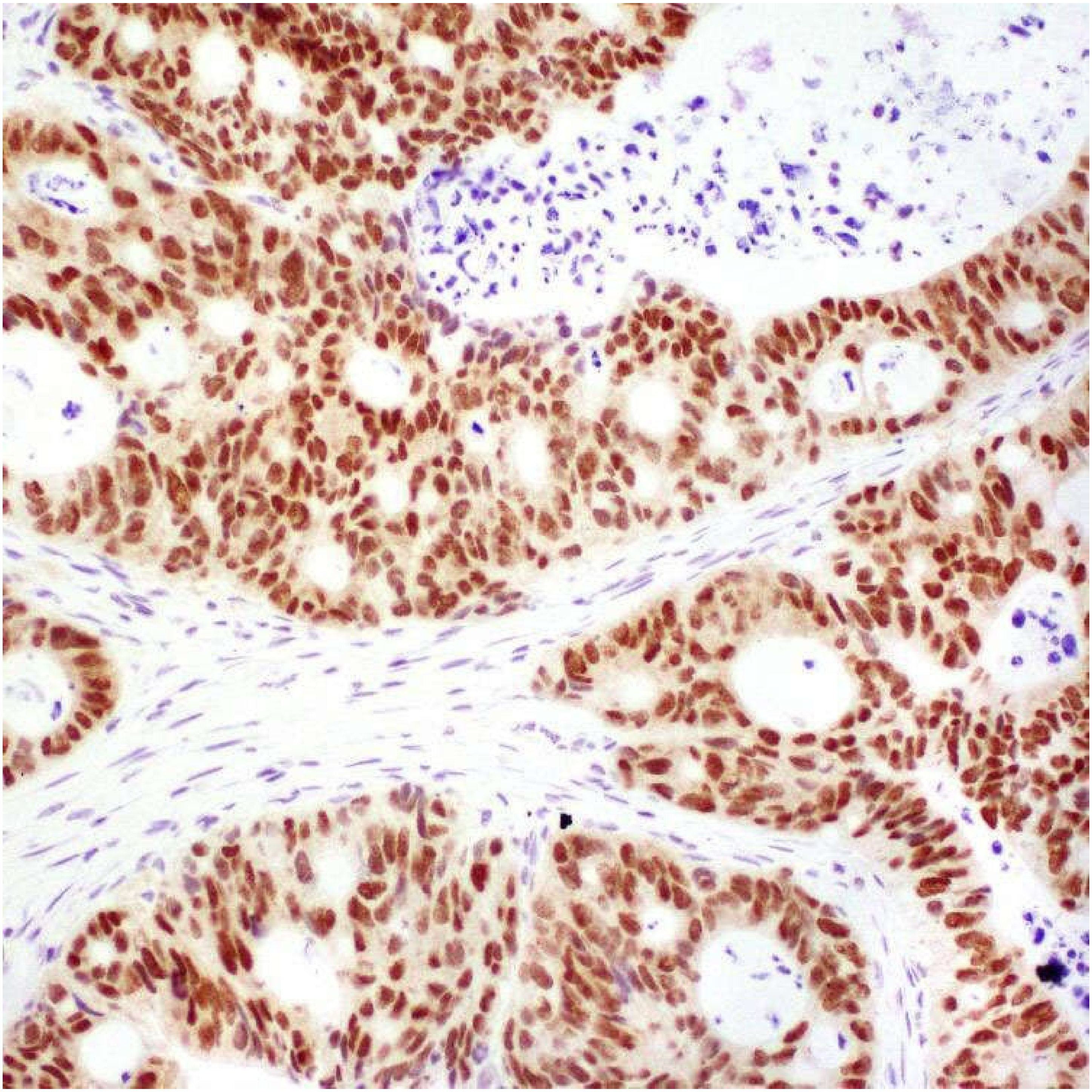


Ampullary Mass
Ampullary adenocarcinoma presents as an exophytic, white mass obstructing the orifice ⇨ of the common bile duct ⇨, which is dilated proximally. The pancreatic duct → is not obstructed.



Intestinal Type

This intestinal-type ampullary adenocarcinoma shows a cribriform pattern with luminal “dirty necrosis” . Tumor cells are columnar with stratified, elongated or oval nuclei, resembling adenocarcinoma of colon and small bowel.



CDX2 Immunostain
Tumor cells in this ampullary adenocarcinoma are positive for CDX-2. They are also positive for CK20 and MUC2 and only focally positive for MUC1 (in < 10% of tumor cells). This immunohistochemical profile is consistent with intestinal type.

TERMINOLOGY

Synonyms

- Periampullary adenocarcinoma

Definitions

- Malignant epithelial neoplasm originating in ampulla of Vater
  - Centered on, circumferentially surrounding, or completely replacing ampulla

ETIOLOGY/PATHOGENESIS

Histogenesis

- Intraampullary: Arise in ampulla (lined by pancreatobiliary epithelium)
- Periampullary: Arise in duodenal surface of papilla (lined by intestinal epithelium)

Predisposing Syndromes

- Familial adenomatous polyposis, Lynch syndrome, type 1 neurofibromatosis

CLINICAL ISSUES

Epidemiology

- Incidence
  - 0.7 and 0.4 cases per 100,000 males and females, respectively
  - 0.5% of all gastrointestinal malignancies
- Age
  - Mean: 62 years (range: 29-85 years)
    - Younger in patients with predisposing syndromes

Presentation

- Jaundice, abdominal pain, pancreatitis, weight loss

Treatment

- Resection (Whipple procedure)
- Chemoradiation therapy

Prognosis

- 5-year overall survival rate: 40%
  - Determined by histologic type, grade, stage, coexisting adenoma
- Intestinal type histology is associated with favorable outcome in comparison to pancreatobiliary type
- CDX-1/2 expression independent marker of favorable outcome

IMAGING

Endoscopic Findings

• Exophytic or ulcerated mass in ampullary region

MACROSCOPIC

General Features

• Exophytic &/or ulcerated mass in ampullary region

MICROSCOPIC

Histologic Features

- Intestinal-type adenocarcinoma
  - Most common type (50-80%)
  - Similar to adenocarcinoma of colon and small bowel
  - Frequently associated with ampullary adenoma
- Pancreatobiliary-type adenocarcinoma
  - 2nd most common type (15-20%)
  - Similar to pancreatic ductal or bile duct adenocarcinoma
  - Micropapillary growth pattern in < 5% of cases
- Mucinous adenocarcinoma
  - ~ 5% of all ampullary carcinomas
  - > 50% of tumor composed of stromal, mucin-containing, floating carcinoma cells
  - May have minor component of signet ring cells
  - Variant of intestinal-type adenocarcinoma
- Signet ring cell carcinoma
  - ~ 2% of all ampullary carcinomas
  - Composed predominantly of signet ring cells with cytoplasmic mucin that pushes nuclei to periphery
- Papillary adenocarcinoma
  - Arise from noninvasive papillary neoplasm
  - Invasive component rarely maintains papillary pattern
- Adenosquamous carcinoma
  - ~ 1% of all ampullary carcinomas
  - Combination of both malignant squamous (> 25%) and glandular (any amount) components
- Undifferentiated carcinoma
  - May be small cell (nonneuroendocrine) or spindle cell predominant
  - Osteoclast-like giant cells are present in rare cases
- Clear cell carcinoma
  - Resembling clear cell renal cell carcinoma
  - Presence of cytoplasmic mucin in some tumor cells
- Hepatoid adenocarcinoma
  - Resembling hepatocellular carcinoma
  - Adenocarcinoma component may be present
- Mixed adenoneuroendocrine carcinoma
  - ≥ 30% of both adenocarcinoma and neuroendocrine carcinoma

ANCILLARY TESTS

Immunohistochemistry

- Intestinal type
    - Positive for CK20, CDX-2, or MUC2, negative for MUC1
    - Positive for CK20, CDX-2, and MUC2, irrespective of MUC1
- Pancreatobiliary type
    - Positive for MUC1, negative for CDX-2 and MUC2

DIFFERENTIAL DIAGNOSIS

Adenocarcinomas of Pancreas, Distal Common Bile Duct, and Duodenum

- Cross sections to include ampulla, duodenum, pancreatic duct and bile duct may help demonstrate relationship of carcinoma to these structures
    - Look for residual ampullary adenoma or noninvasive papillary neoplasm
    - Colonization of ampullary mucosa by invasive carcinoma of pancreas or bile duct can occur

Pancreatic Adenocarcinoma

- Vast majority exhibit pancreatobiliary-type histology
- Pancreatic adenocarcinoma usually arises from main pancreatic duct; ampullary involvement represents peripheral extension
- No associated ampullary adenoma

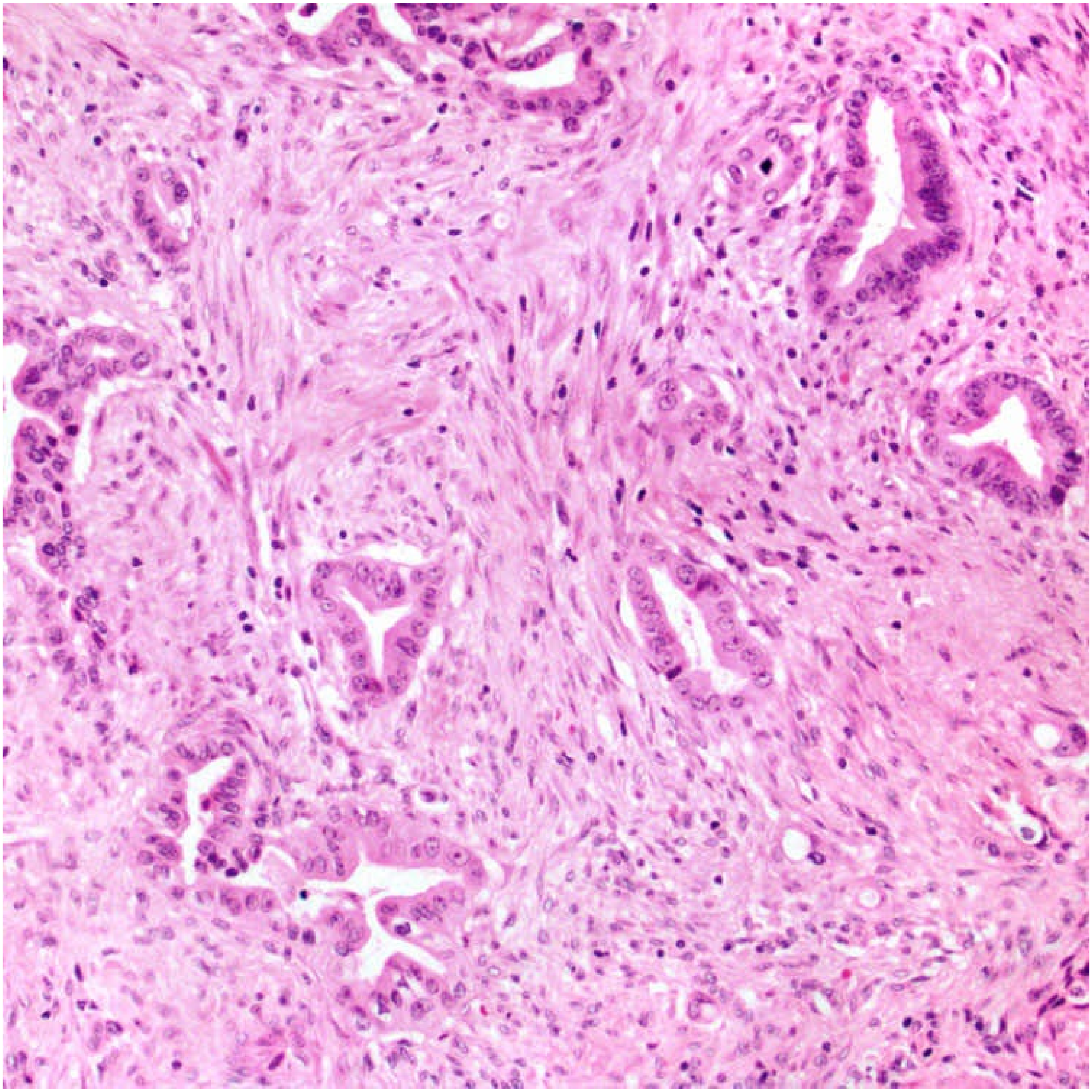
DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Important to distinguish intestinal type from pancreatobiliary type because of more favorable prognosis
    - Classified according to predominant component

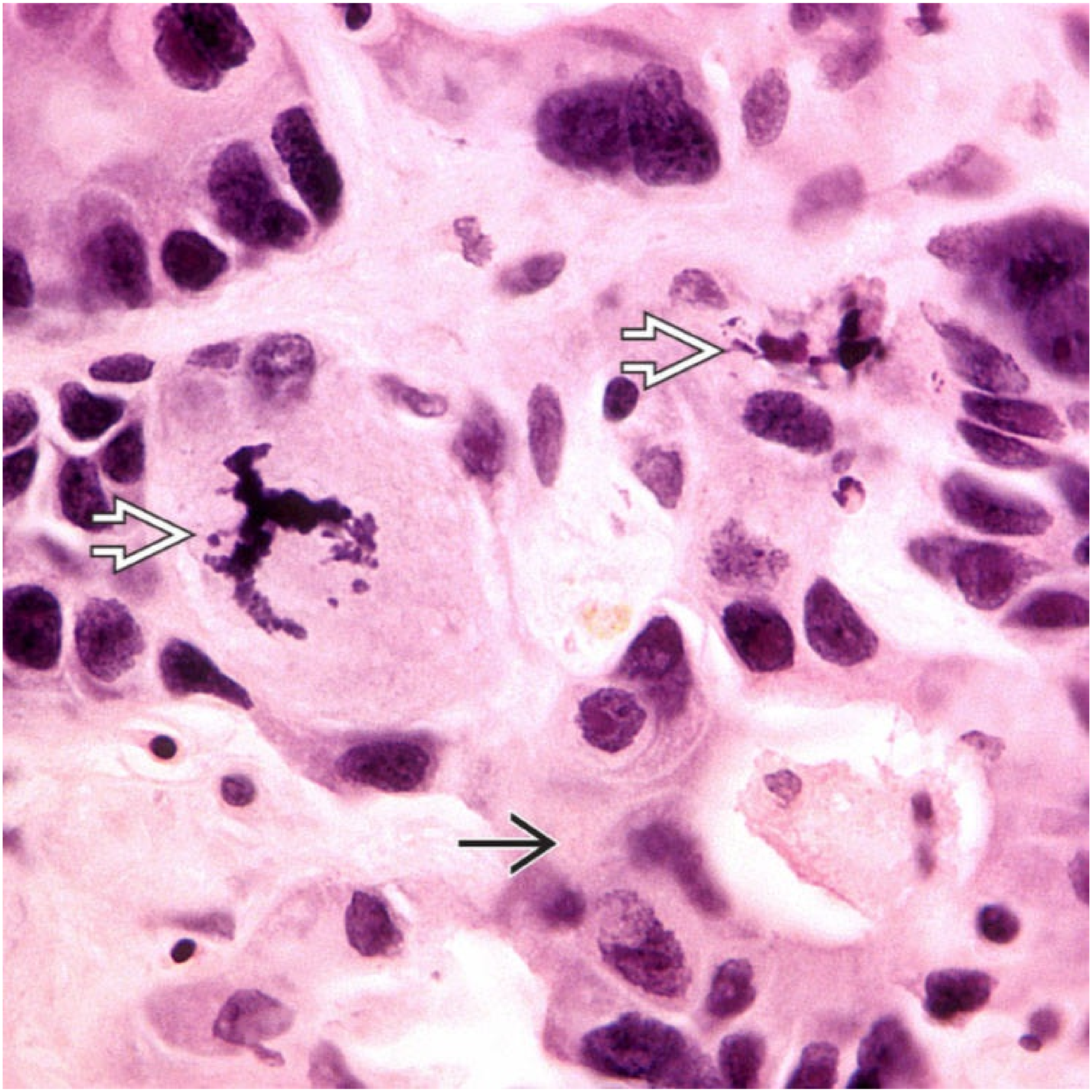
Pathologic Interpretation Pearls

- Cross sections including ampulla, pancreatic duct, and bile duct may help demonstrate relationship of carcinoma to these structures



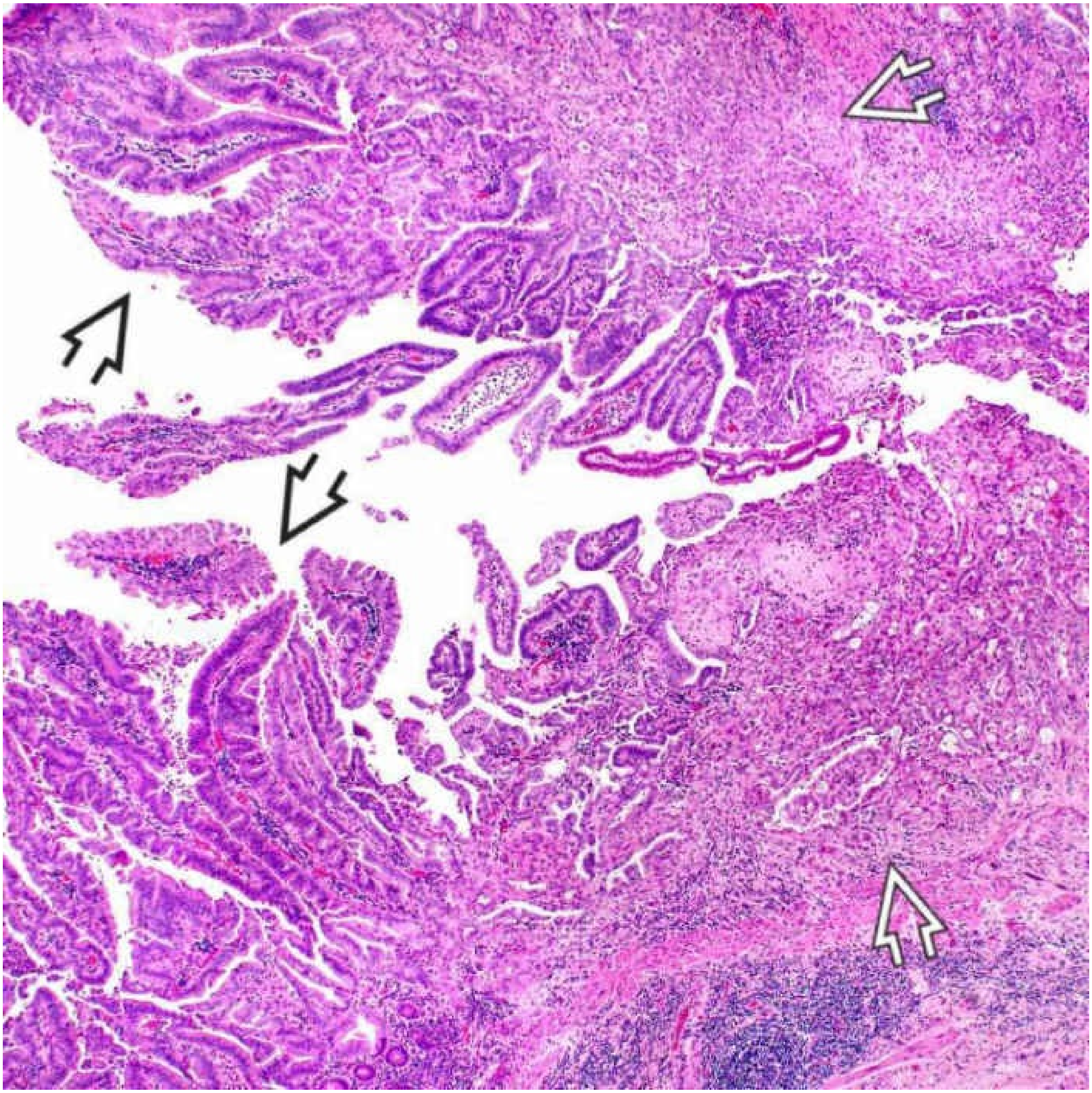
Pancreatobiliary Type

Pancreatobiliary-type ampullary adenocarcinoma shows well-formed tubules in abundant desmoplastic stroma. The tubules are lined by a single layer of cuboidal to low columnar cells.

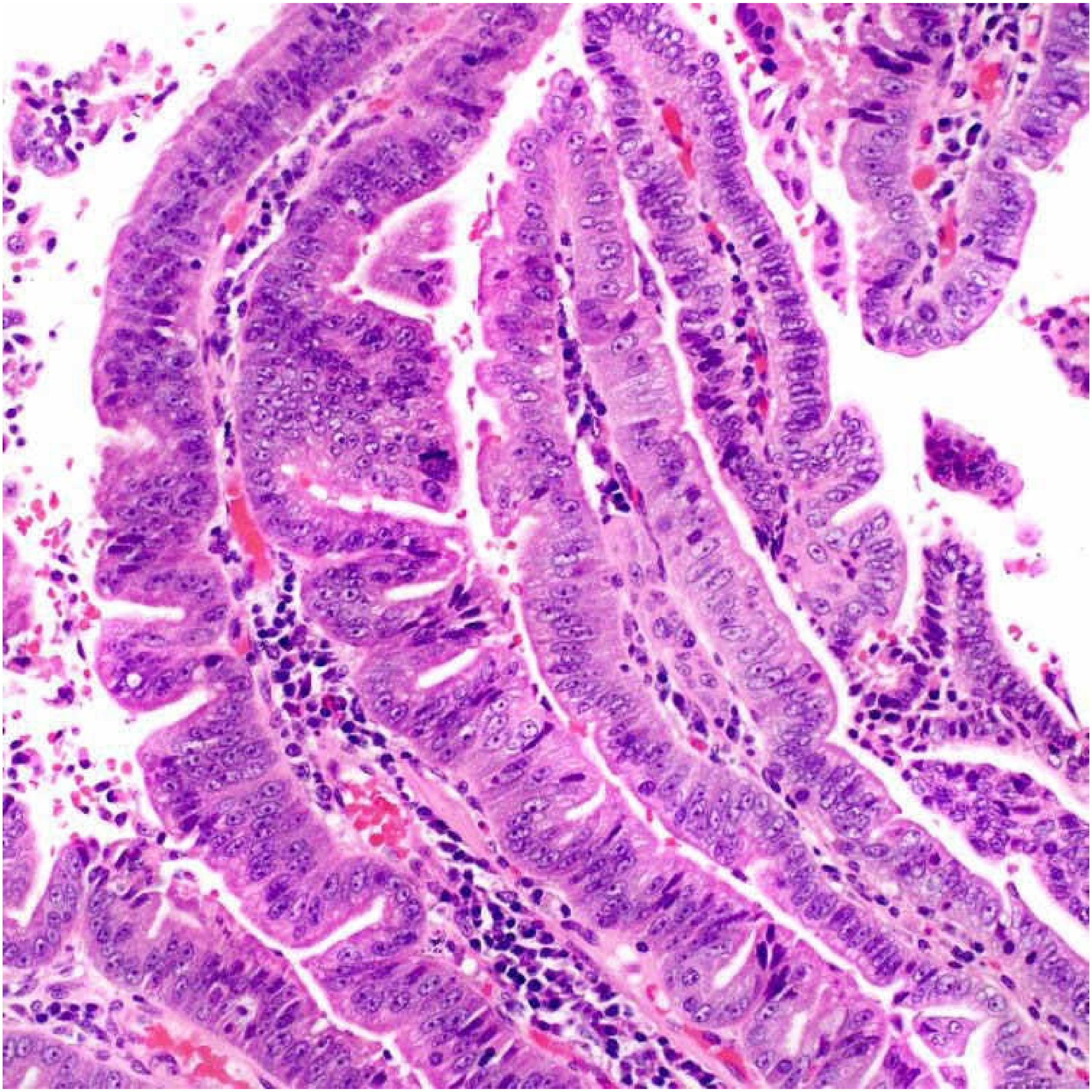


Pancreatobiliary Type

Pancreatobiliary-type ampullary adenocarcinoma shows prominent nuclear pleomorphism and frequent atypical mitoses ⇨. Glandular formation is noted →. In general, pancreatobiliary type shows greater nuclear atypia and more mitoses than intestinal type.

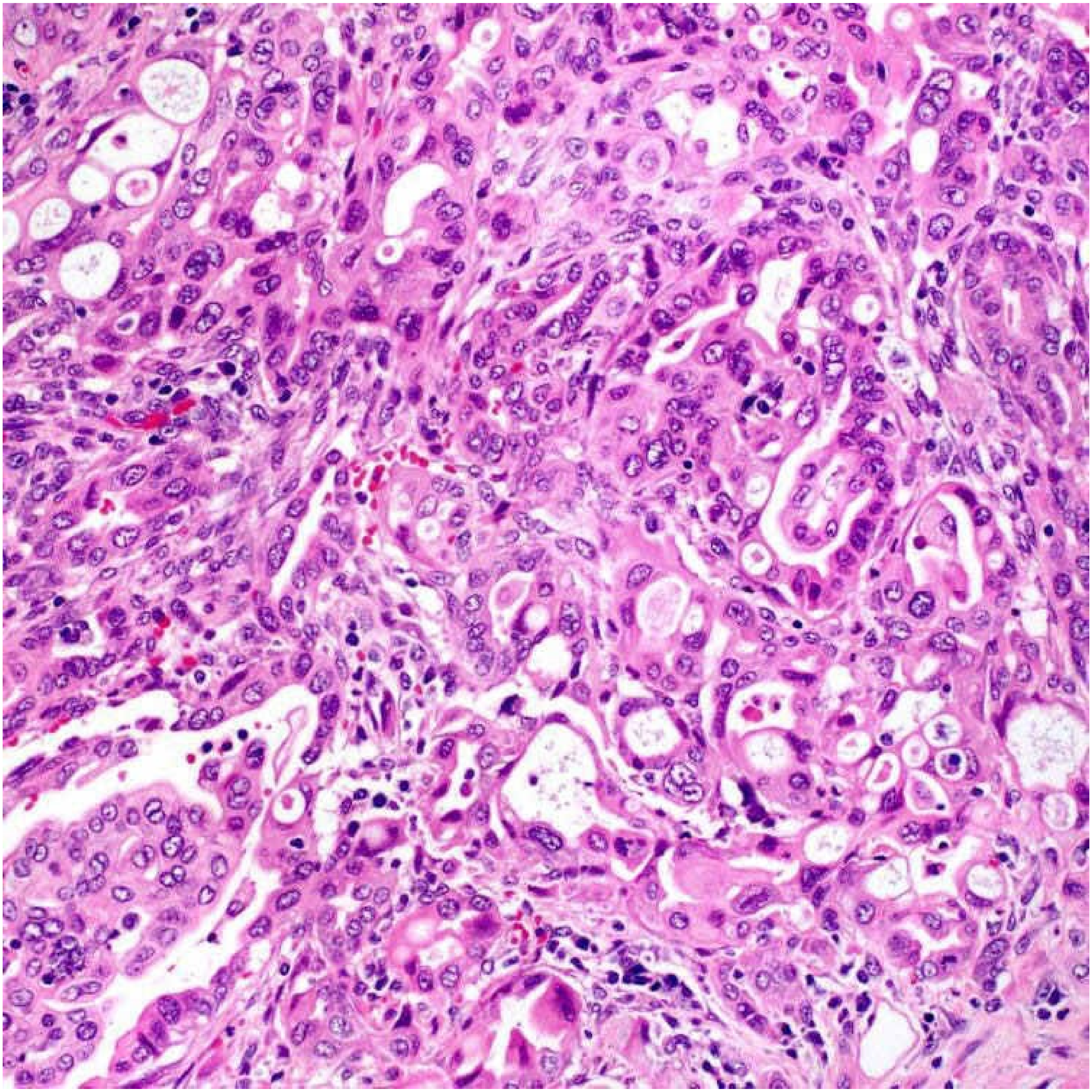


Papillary Adenocarcinoma
Low-power view of this exophytic ampullary mass shows invasive adenocarcinoma arising from papillary neoplasm .

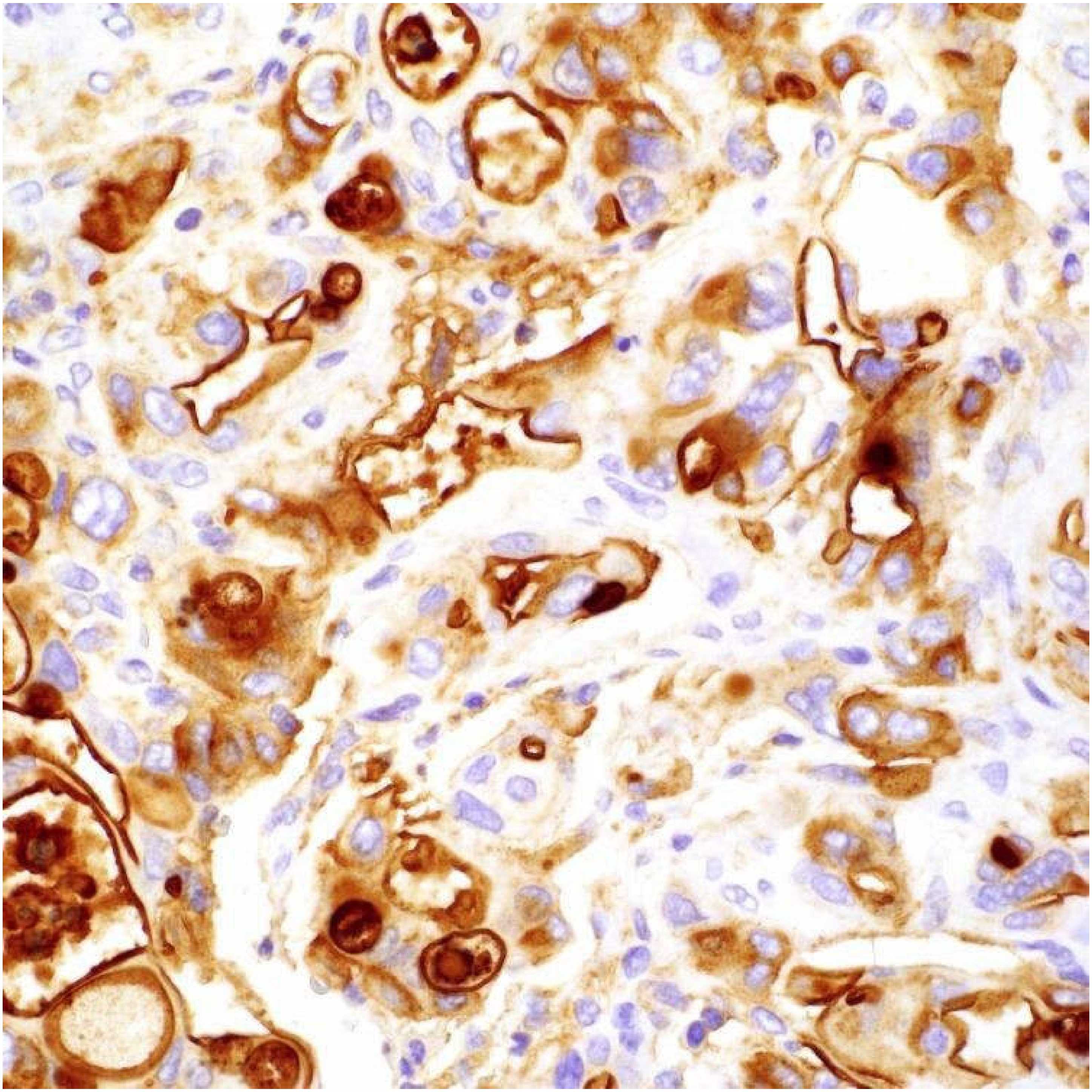


Noninvasive Papillary Neoplasm

Noninvasive papillary neoplasm on the surface of this ampullary mass shows a papillary architecture. Tumor cells have round or oval stratified/pseudostratified nuclei and discernible nucleoli. It is morphologically similar to intracystic/intraductal papillary neoplasms seen in gallbladder and extrahepatic bile ducts.

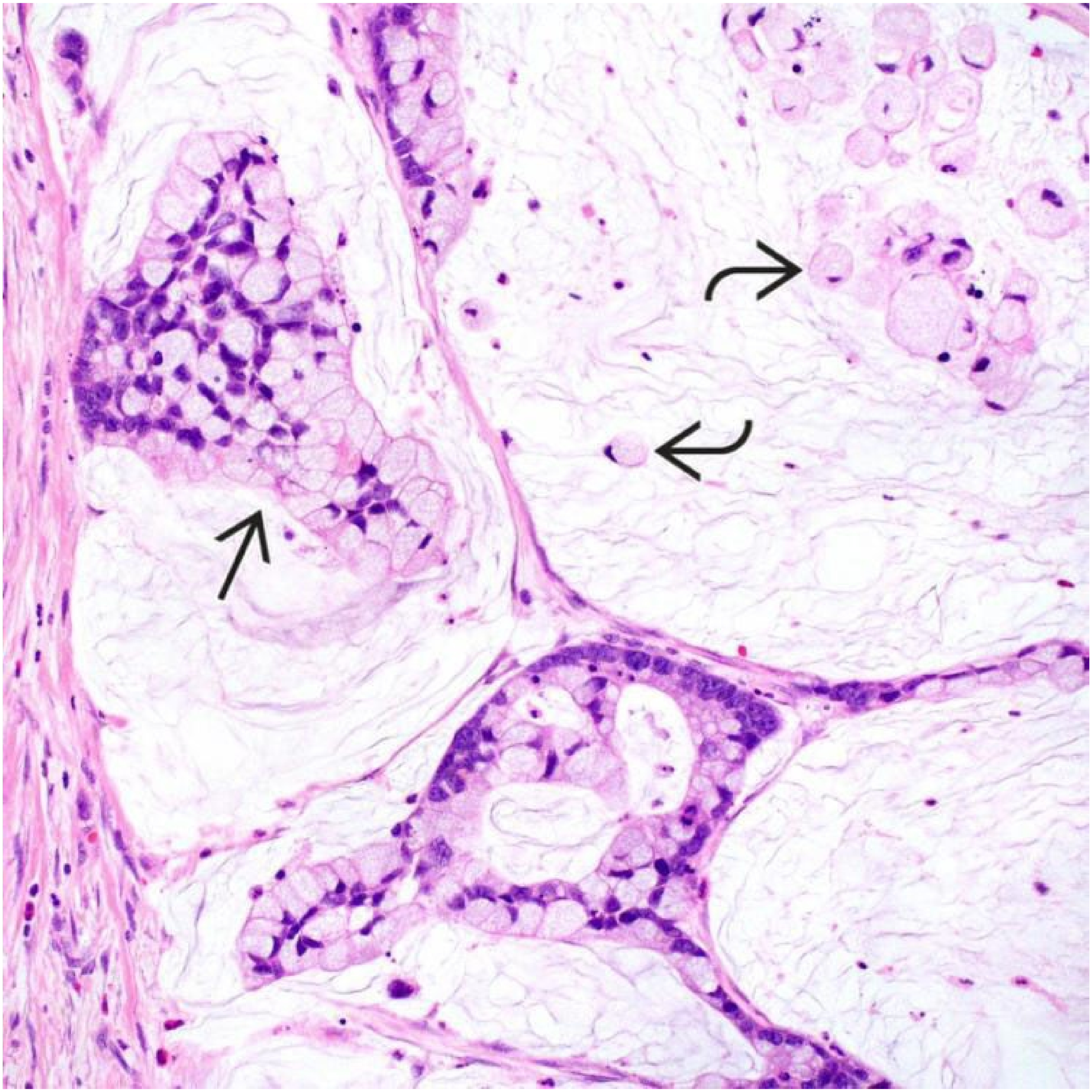


Invasive Papillary Adenocarcinoma
The invasive component in this case of papillary adenocarcinoma of the ampulla is of pancreatobiliary type. It can also be intestinal type, however. No papillary architecture is noted in invasive component in this case.

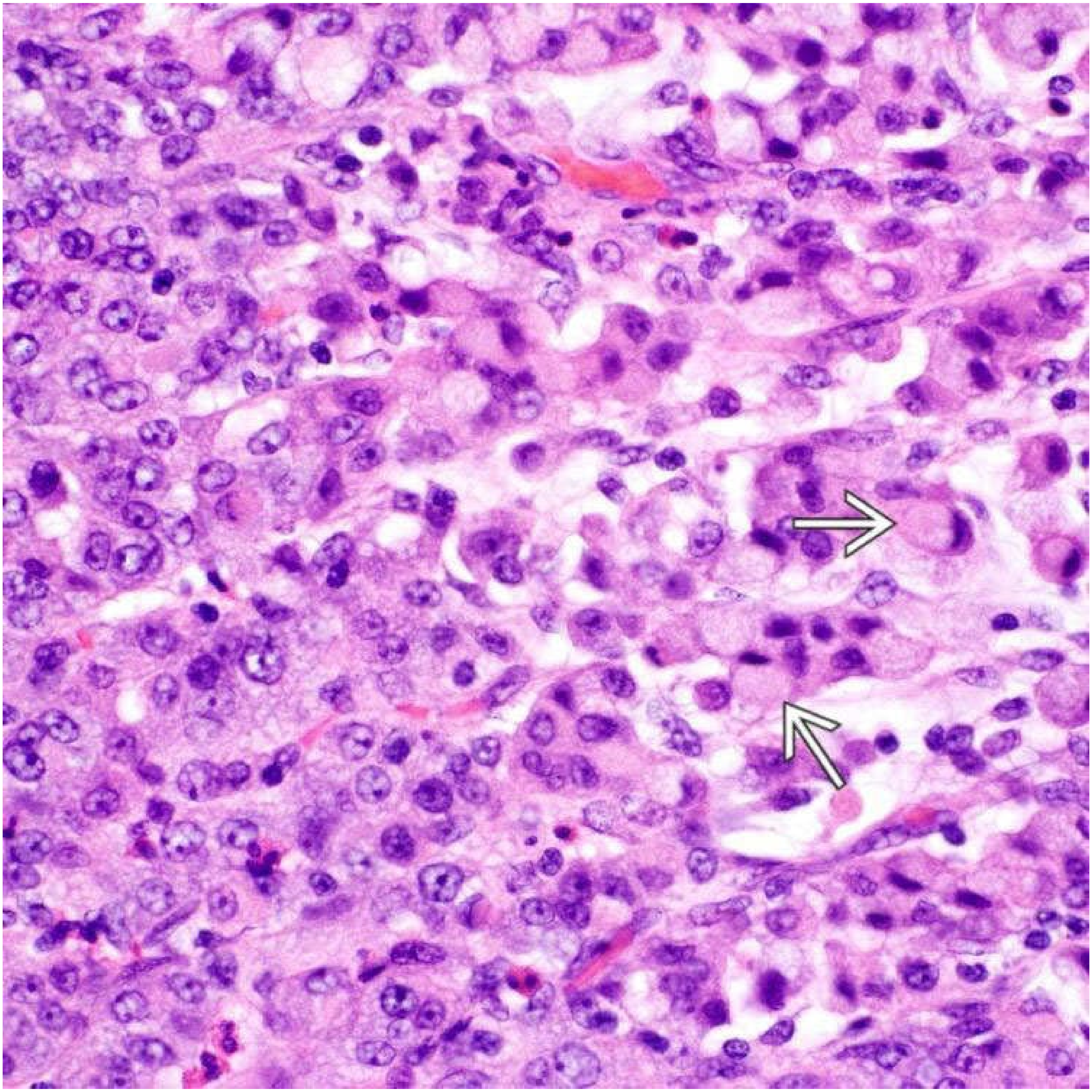


MUC1 Immunostain

Tumor cells in this case of invasive papillary adenocarcinoma of ampulla stain positive for MUC1, but do not react to antibodies for MUC2 and CDX-2. This immunohistochemical profile is consistent with pancreatobiliary type.

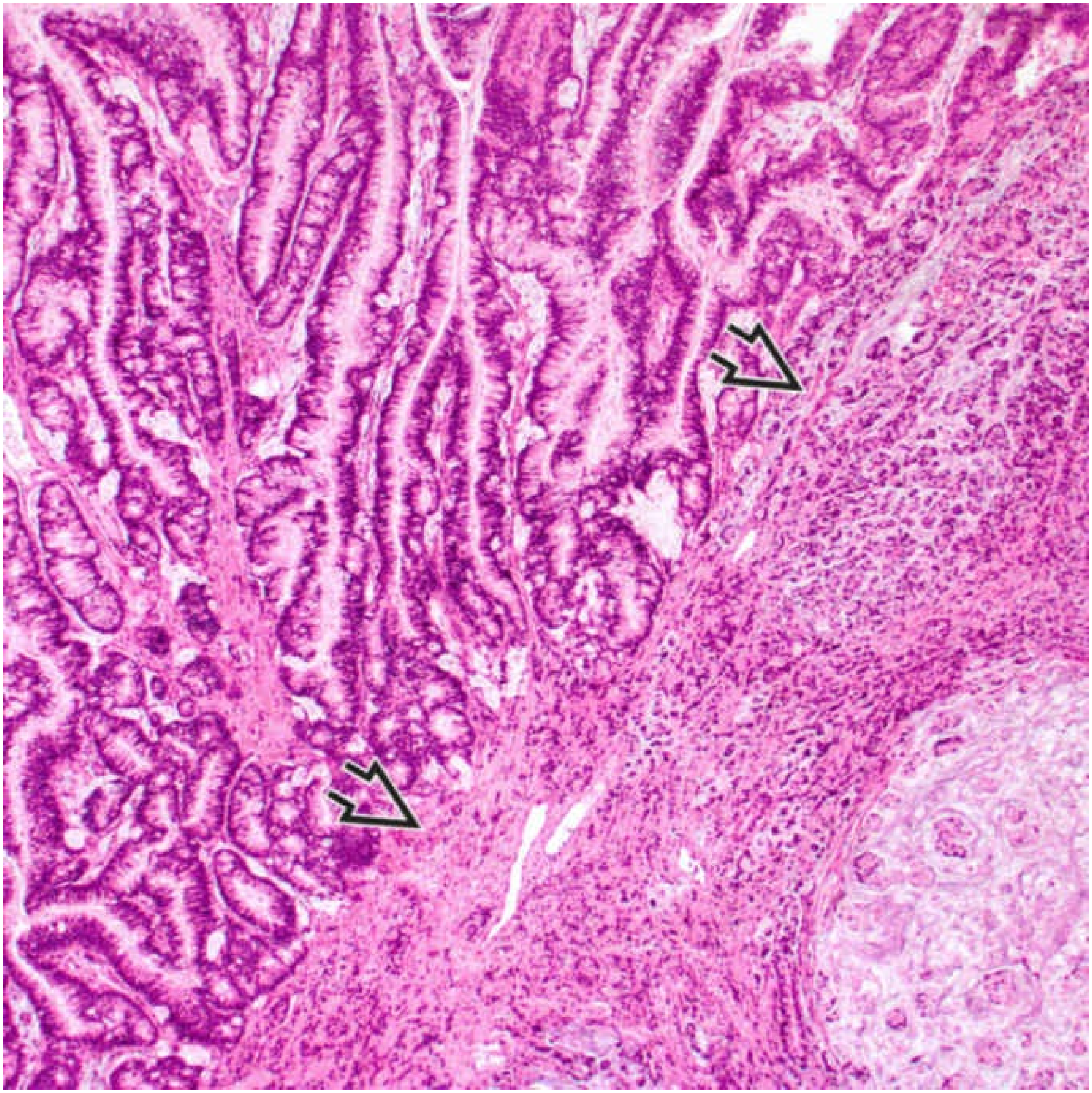


Mucinous Adenocarcinoma
This case of ampullary adenocarcinoma shows abundant extracellular mucin with clusters of tumor cells floating in mucin pools →. Floating signet ring cells are also noted in this field ↱. Intracytoplasmic mucin is evident in tumor cells.



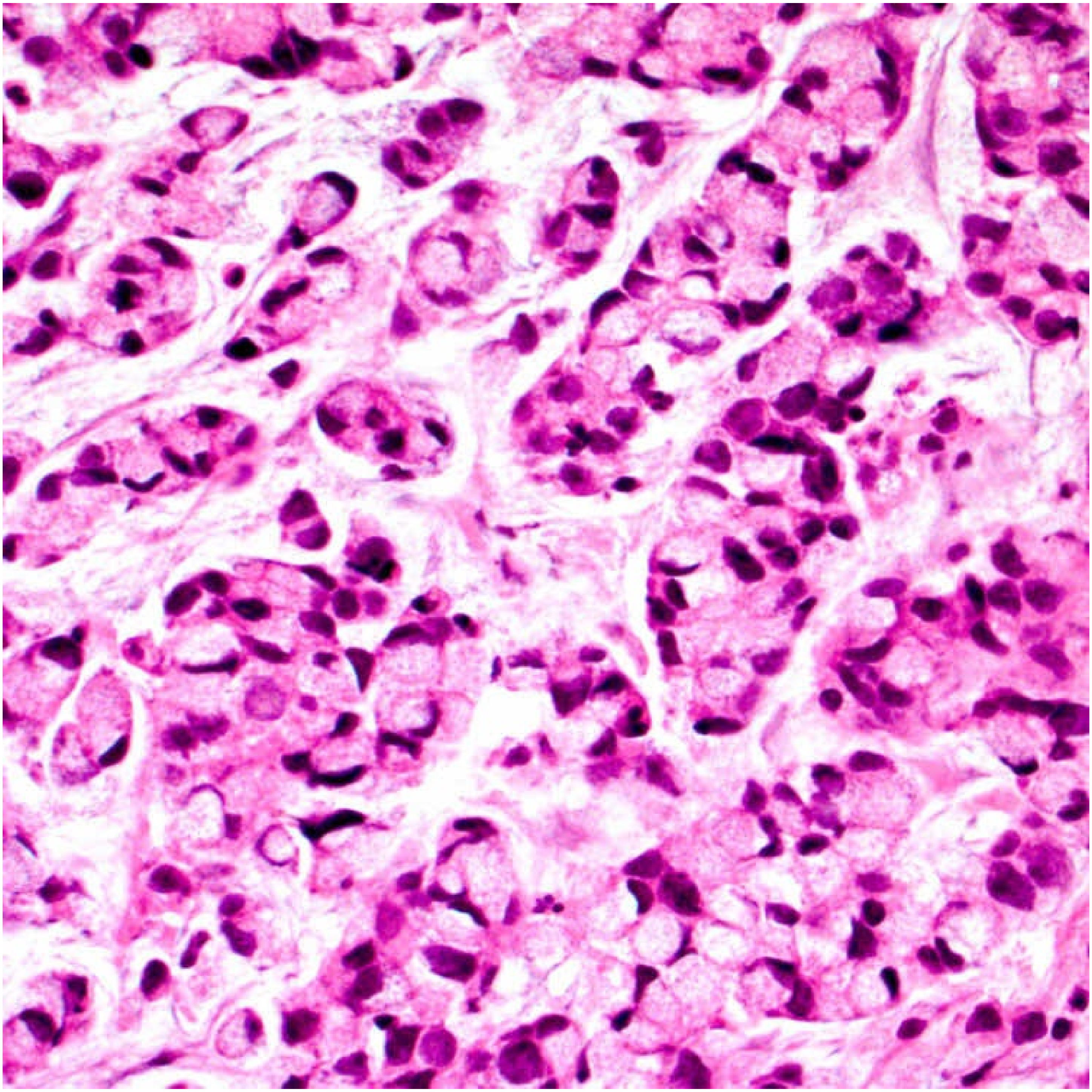
Poorly Differentiated Adenocarcinoma

This poorly differentiated ampullary adenocarcinoma shows sheets of neoplastic cells with no overt glandular formation. Signet ring cells ⇒ are present but they account for only a small tumor volume, which is insufficient for a diagnosis of signet ring cell carcinoma.

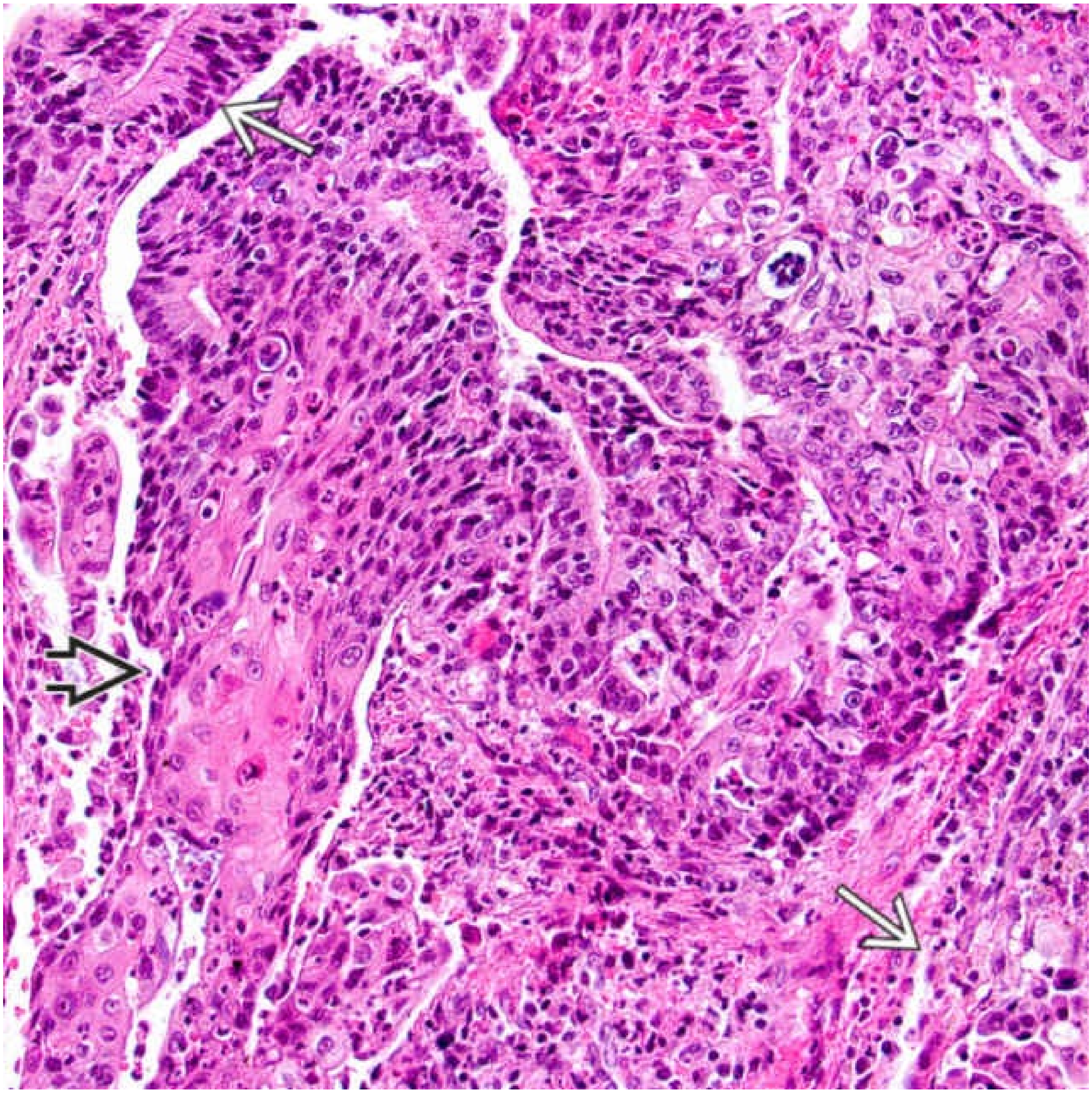


Adenocarcinoma Arising From Adenoma

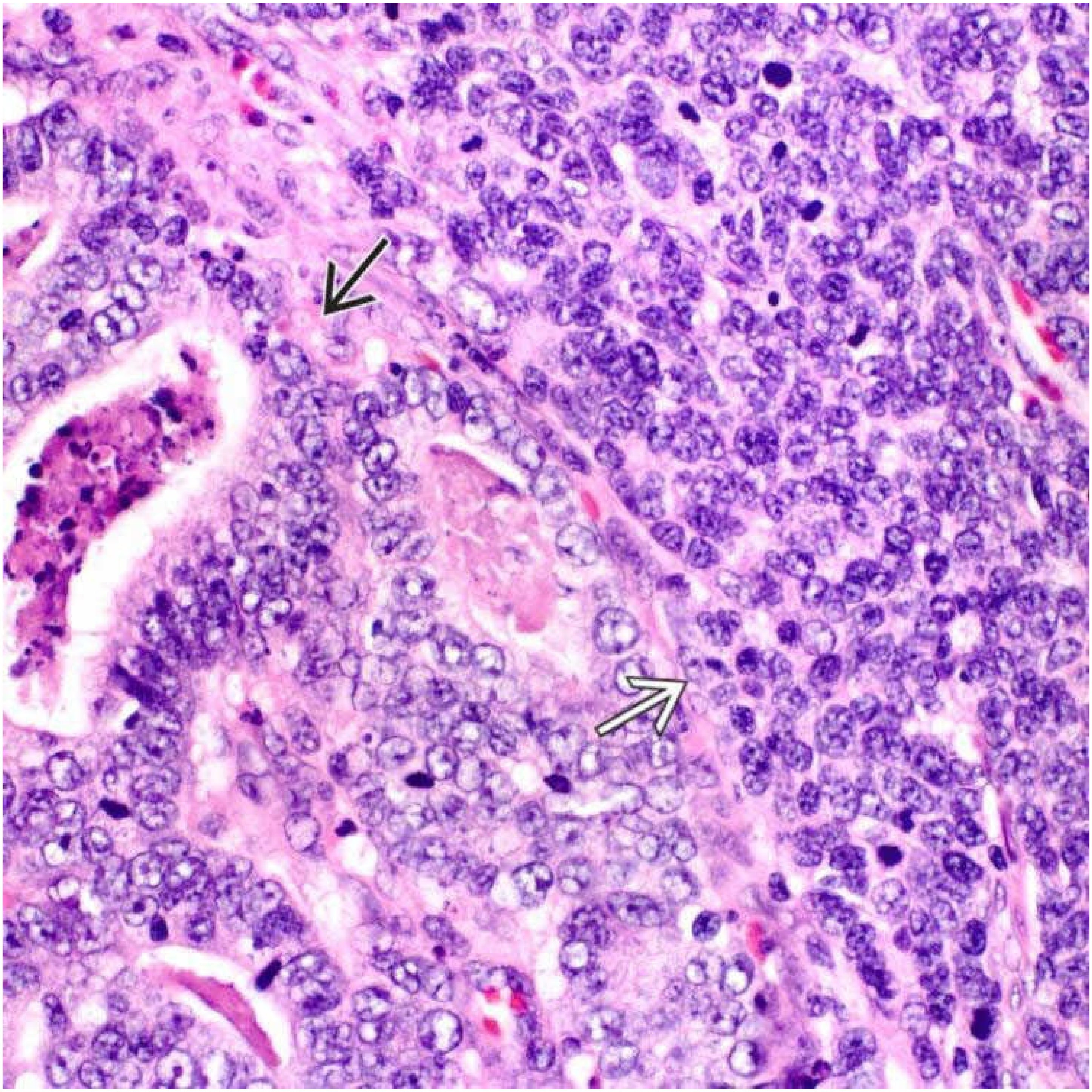
Ampullary adenocarcinoma ➪ is associated with a large, intestinal-type adenoma. This association is usually seen for intestinal-type adenocarcinoma and only occasionally seen for pancreatobiliary type.



Signet Ring Cell Carcinoma
Ampullary adenocarcinoma shows abundant signet ring cells with a diffuse, infiltrative growth pattern. Tumor cells are present in clusters or individually and have cytoplasmic mucin that pushes nuclei aside. Extracellular mucin is usually inconspicuous.



Adenosquamous Carcinoma
Ampullary carcinoma contains components of squamous cell carcinoma ➩ and adenocarcinoma ⇨. The adenocarcinoma component is usually of pancreatobiliary type.



Mixed Adenoneuroendocrine Carcinoma
Ampullary carcinoma contains components of gland-forming adenocarcinoma → and small cell neuroendocrine carcinoma ⇨. Both components need to be at least 30%. Detection of scattered neuroendocrine cells by immunohistochemistry in an otherwise conventional adenocarcinoma does not qualify for this diagnosis.

SELECTED REFERENCES

1. Senatore, FJ, et al. Adenocarcinoma of the ampulla of Vater: what treatment options are available? *J Oncol Pharm Pract*. 2015; 21(5):364–369.
2. Ang, DC, et al. The utility of immunohistochemistry in subtyping adenocarcinoma of the ampulla of vater. *Am J Surg Pathol*. 2014; 38(10):1371–1379.

3.Perysinakis, I, et al. Ampullary cancer–a separate clinical entity? *Histopathology*. 2014; 64(6):759–768.

Well-Differentiated Neuroendocrine Tumor, Ampulla

KEY FACTS

Terminology

- Low- to intermediate-grade neoplasms with predominantly neuroendocrine differentiation arising in ampulla of Vater and periampullary region

Etiology/Pathogenesis

- Association with neurofibromatosis type 1 and multiple endocrine neoplasia type 1 in some cases

Clinical Issues

- 82% and 71% 5- and 10-year survival rates, respectively, for patients with low-grade tumors

Microscopic

- Tumor cells arranged in nested, trabecular, insular, glandular, or cribriform patterns
- Small, uniform tumor cells with round nuclei, salt and pepper chromatin, inconspicuous nucleoli, and moderate amounts of granular eosinophilic cytoplasm
- Variable mitotic activity, but < 20 per 10 HPF

Ancillary Tests

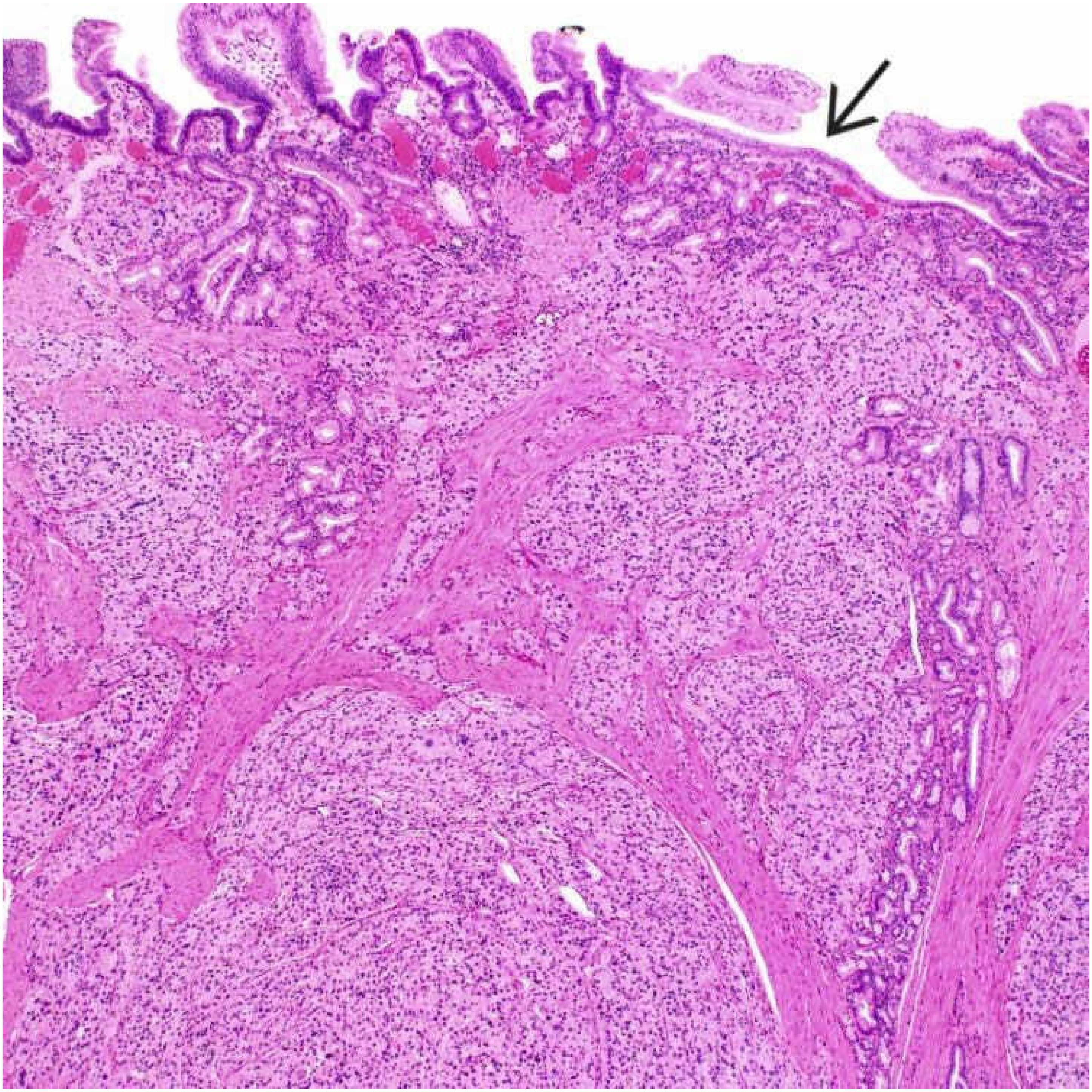
- Positive for neuroendocrine markers synaptophysin and chromogranin
- Immunohistochemical detection of hormone production for tumor classification is not recommended

Top Differential Diagnoses

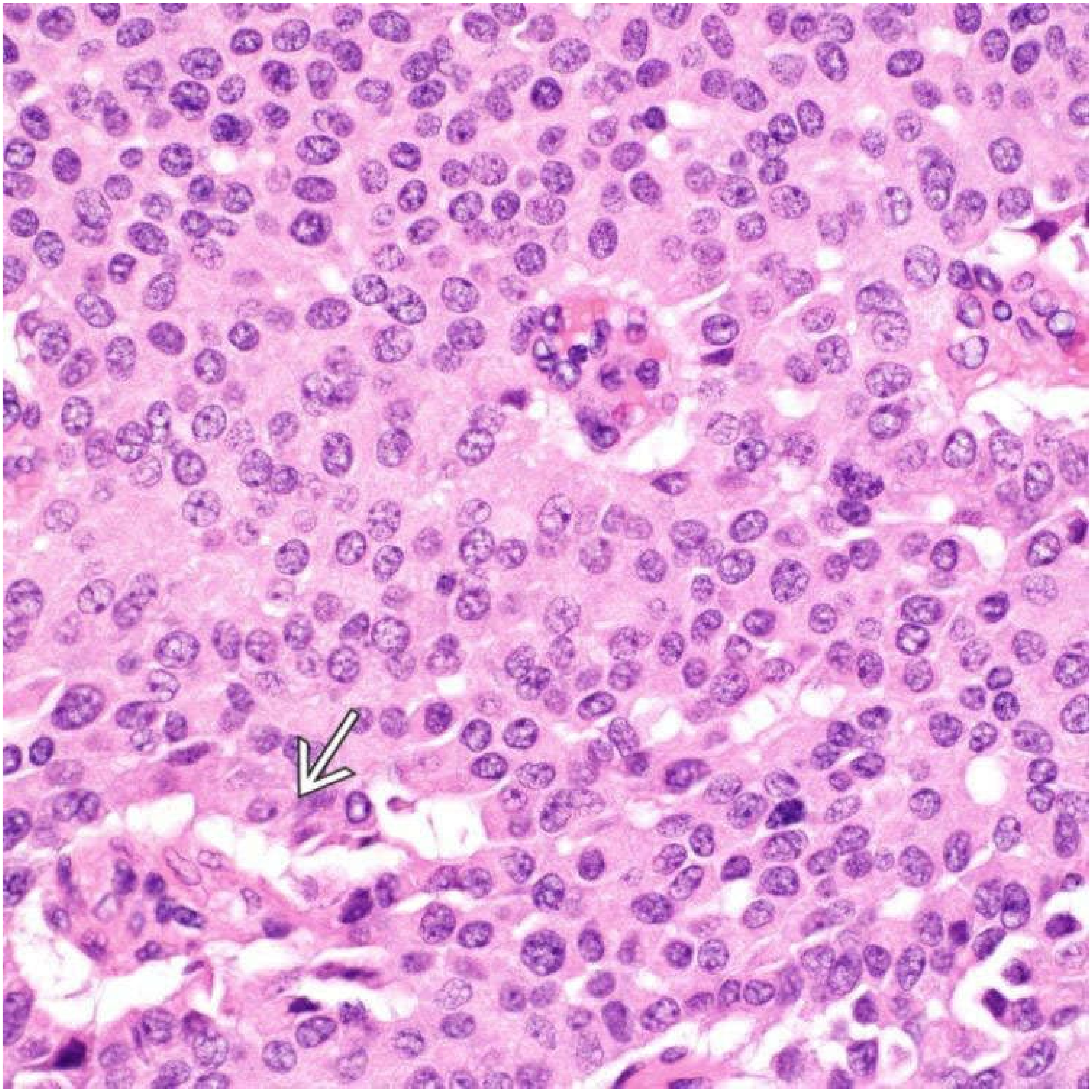
- Adenocarcinoma
- Gangliocytic paraganglioma

Grading

- Grade 1 (low): Mitosis < 2 per 10 HPF, and Ki-67 < 3 %
  - Grade 2 (intermediate): Mitosis 2-20 per 10 HPF, &/or Ki-67 3-20%
  - Grade 3 (high): Mitosis > 20 per 10 HPF, &/or Ki-67 > 20%
  - Grade 3 tumors: Poorly differentiated neuroendocrine carcinoma (small or large cell type)

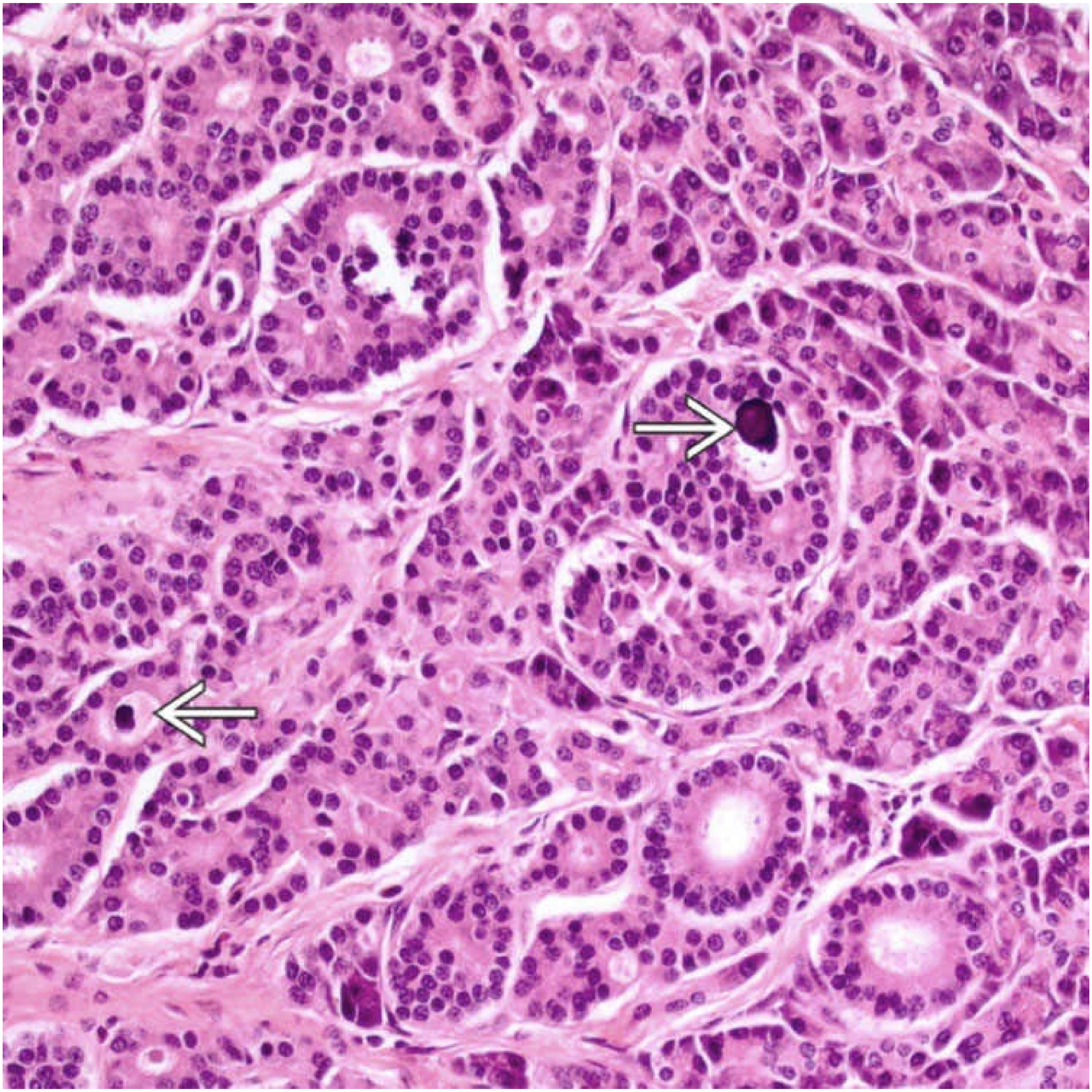


Tumor in Ampullary Region
Low-power view shows a well-differentiated neuroendocrine neoplasm infiltrating the ampullary region. The overlying mucosa is attenuated and shows gastric foveolar metaplasia →.

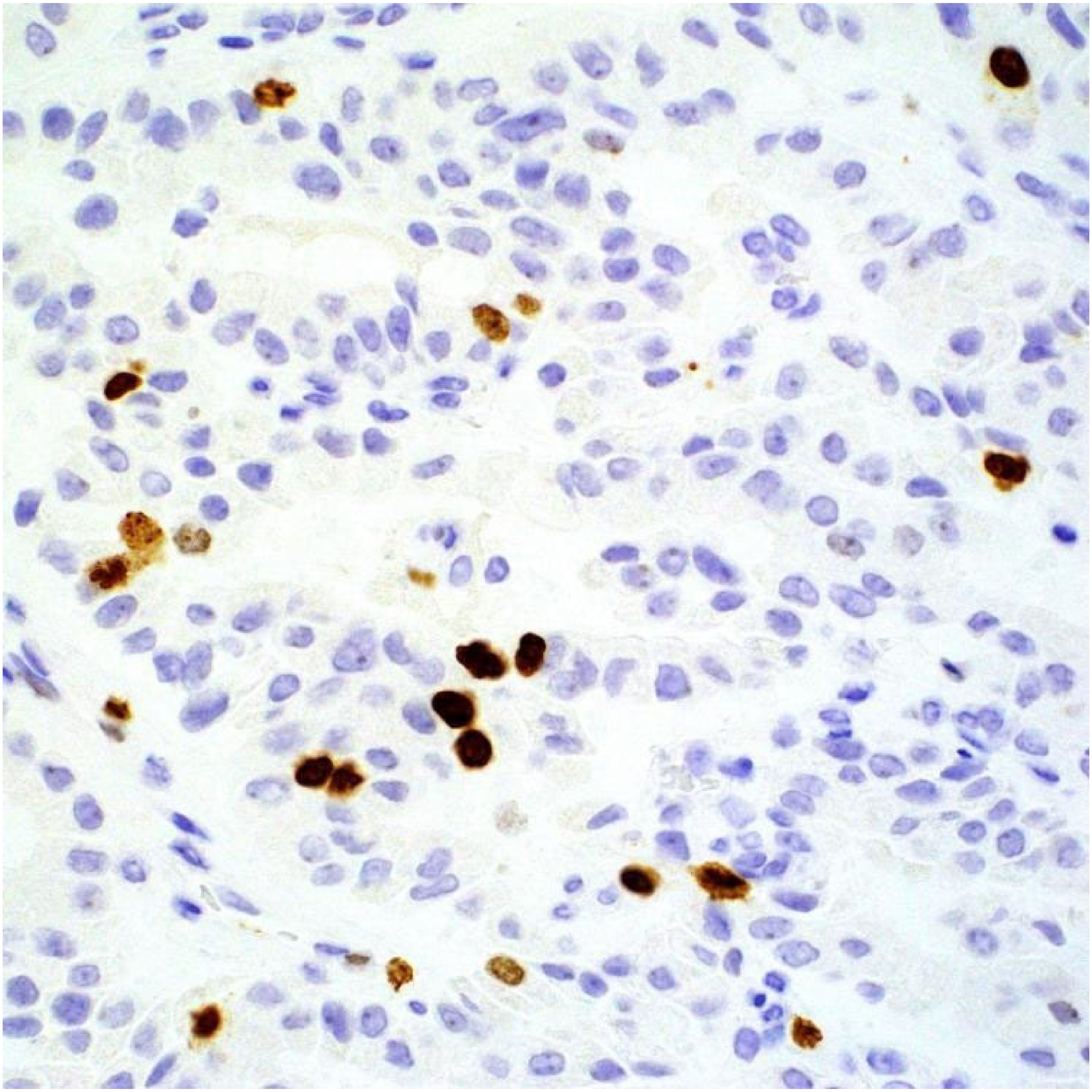


Histologic Features

Tumor cells are typically uniform with round nuclei, salt and pepper chromatin, inconspicuous nuclei, and moderate amounts of eosinophilic cytoplasm. Focal glandular formation ⇒ is noted. Mitotic figures are difficult to find.



Psammoma Bodies
Well-differentiated neuroendocrine neoplasm of the ampulla shows extensive glandular formation. Psammomatous calcifications are noted in the lumina of some of the glands ⇒. These features are more commonly seen in somatostatin-producing tumors.



Ki-67 Index

Well-differentiated neuroendocrine neoplasm of the ampulla shows positive immunostain for Ki-67 in ~ 5% of tumor cells. The tumor is thus graded as intermediate (grade 2), even though the mitotic rate is < 2 per 10 HPF.

TERMINOLOGY

Abbreviations

- Well-differentiated neuroendocrine neoplasm (WDNEN)

Synonyms

- Well-differentiated neuroendocrine tumor

- Carcinoid tumor (not preferred)

Definitions

- Low- to intermediate-grade neoplasms with predominantly neuroendocrine differentiation arising in ampulla of Vater and periampullary region

ETIOLOGY/PATHOGENESIS

Disease Association

- Neurofibromatosis type 1
  - Somatostatin-producing tumors are most common
- Multiple endocrine neoplasia type 1
  - Gastrin-producing tumors are most common
- *Helicobacter pylori* infection

CLINICAL ISSUES

Epidemiology

- Incidence
  - < 1% of all gastrointestinal neuroendocrine neoplasms
  - < 2% of all tumors of ampullary region
- Age
  - Mean: 62 years
- Sex
  - No sex predilection

Presentation

- Obstructive jaundice, pancreatitis, abdominal pain
- Hormonal hypersecretion syndromes are extremely rare
- Asymptomatic, incidentally discovered

Treatment

- Pancreaticoduodenectomy (Whipple procedure)
- Local excision (ampullectomy) in selected cases

Prognosis

- Tumor grade and distal metastasis are most useful predictors
  - 82% and 71% 5- and 10-year survival rates, respectively, for patients with low-grade tumors
- Tumor size does not predict metastatic potential

IMAGING

CT and Octreotide Scan

- Help metastatic work-up once diagnosis is established

MACROSCOPIC

General Features

- Solitary submucosal polypoid lesion or bulge with intact or flattened mucosa
- Mean size: 1.8 cm (range: 0.2-5.0 cm)

MICROSCOPIC

Histologic Features

- Tumor cells arranged in nested, trabecular, insular, glandular, or cribriform patterns
  - Somatostatin-producing tumors may show predominantly glandular pattern
    - Psammoma bodies may be present in glandular lumina in some cases
- Small, uniform tumor cells with round nuclei, salt and pepper chromatin, inconspicuous nucleoli, and moderate amounts of granular eosinophilic cytoplasm
- Variable mitotic activity, but < 20 per 10 HPF
- Punctate necrosis may be seen
- Amyloid deposition may occur occasionally

ANCILLARY TESTS

Immunohistochemistry

- Positive for neuroendocrine markers synaptophysin and chromogranin
  - Chromogranin is positive in only 50% of somatostatin-producing tumors
- Positive for pankeratin
- Immunohistochemical detection of hormone production for tumor classification is not recommended
  - Does not correlate with clinical syndromes
  - Prognosis is primarily based on histologic grade
  - Majority of neuroendocrine tumors are nonfunctional

DIFFERENTIAL DIAGNOSIS

Adenocarcinoma

- More pronounced nuclear atypia
- More brisk mitotic activity

- Negative or only focally positive for neuroendocrine markers

Gangliocytic Paraganglioma

- Triphasic elements including ganglion or ganglion-like cells, spindled cells with Schwannian differentiation, and epithelioid neuroendocrine cells
  - S100 immunostain is helpful
  - Highlights spindled cells and sustentacular network surrounding neuroendocrine cell nests

Adenocarcinoid

- Mixed adenocarcinoma/WDNEN tumor
- Entrapped ductules in WDNEN may mimic adenocarcinoid

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Somatostatin-producing endocrine cells are normally present in ampullary region

GRADING

Mitotic Rate and Ki-67 Labeling Index

- Grade 1 (low): Mitosis < 2 per 10 HPF, and Ki-67 < 3%
  - Grade 2 (intermediate): Mitosis 2-20 per 10 HPF, &/or Ki-67 3-20%
  - Grade 3 (high): Mitosis > 20 per 10 HPF, &/or Ki-67 > 20%
  - Grade 1 and 2 tumors: Well-differentiated neuroendocrine neoplasm
  - Grade 3 tumors: Poorly differentiated neuroendocrine carcinoma (small or large cell type)
- Recommendation
  - Mitotic rate: Counting 50 HPF in areas with highest mitotic activity
  - Ki-67 index: Counting 500-2,000 tumor cells in areas with highest nuclear labeling

SELECTED REFERENCES

1. Jayant, M, et al. Neuroendocrine tumors of the ampulla of vater: presentation, pathology and prognosis. *JOP*. 2012; 13(3):263–267.
2. Albores-Saavedra, J, et al. Carcinoids and high-grade neuroendocrine carcinomas of the ampulla of vater: a comparative analysis of 139 cases from the surveillance, epidemiology, and end results program-a population based study. *Arch Pathol Lab Med*. 2010; 134(11):1692–1696.

Paraganglioma

KEY FACTS

Terminology

- Gangliocytic paraganglioma
- Uncommon (~ 1% of ampullary neoplasms)
- Some cases associated with neurofibromatosis type 1

Etiology/Pathogenesis

- Several theories
  - Progenitor neural crest cells
  - Embryonic celiac ganglion
  - Endodermally derived epithelial cells originating from ventral primordium of pancreas (hamartomatous proliferation)
  - Pancreatic tumor composed of ganglion-islet cell complexes

Clinical Issues

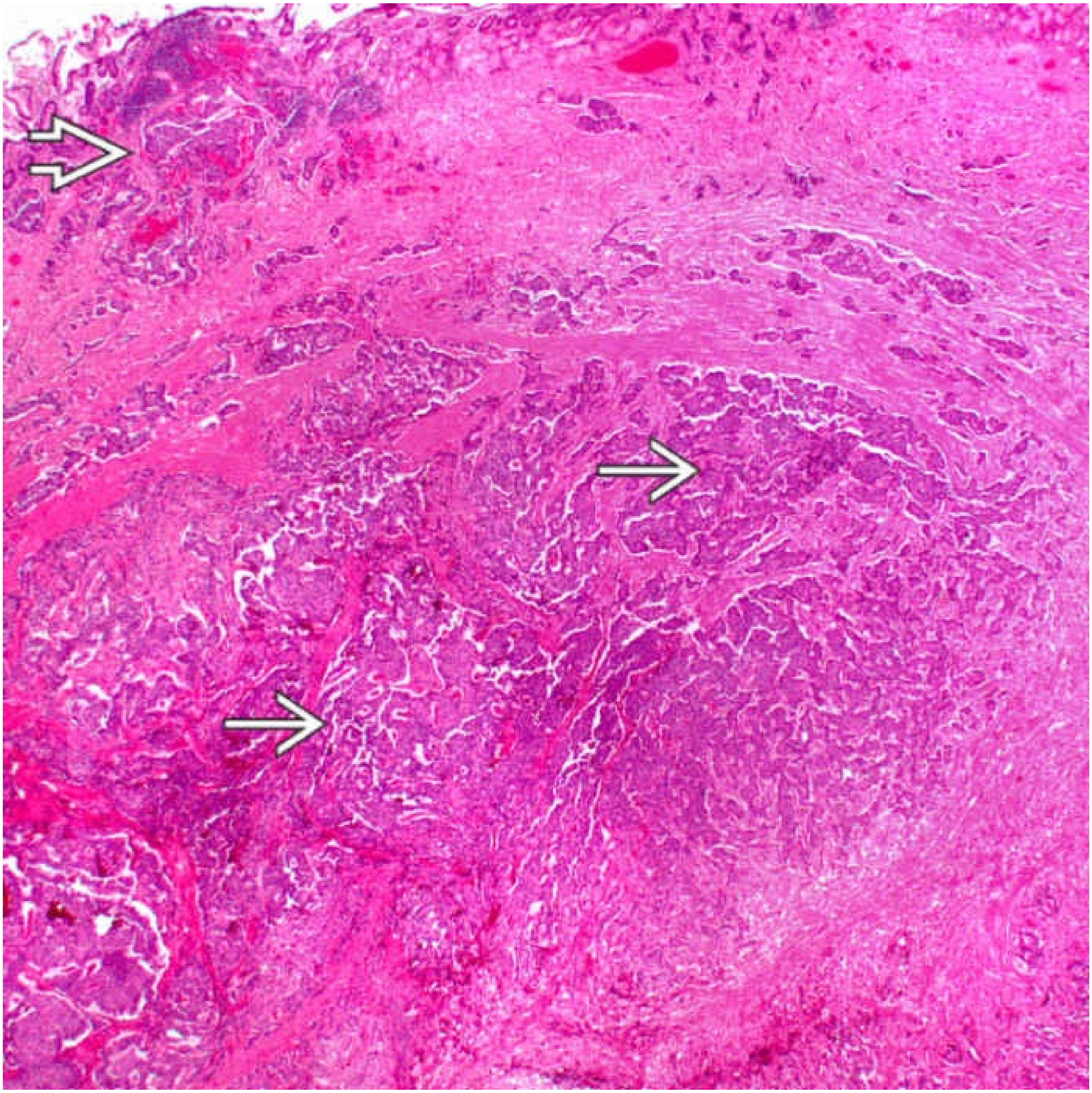
- Uncommon
- 3rd-9th decades (mean age: 6th decade)
- Men slightly out number women
- Most commonly involve periampullary duodenum
- Clinically benign

Microscopic

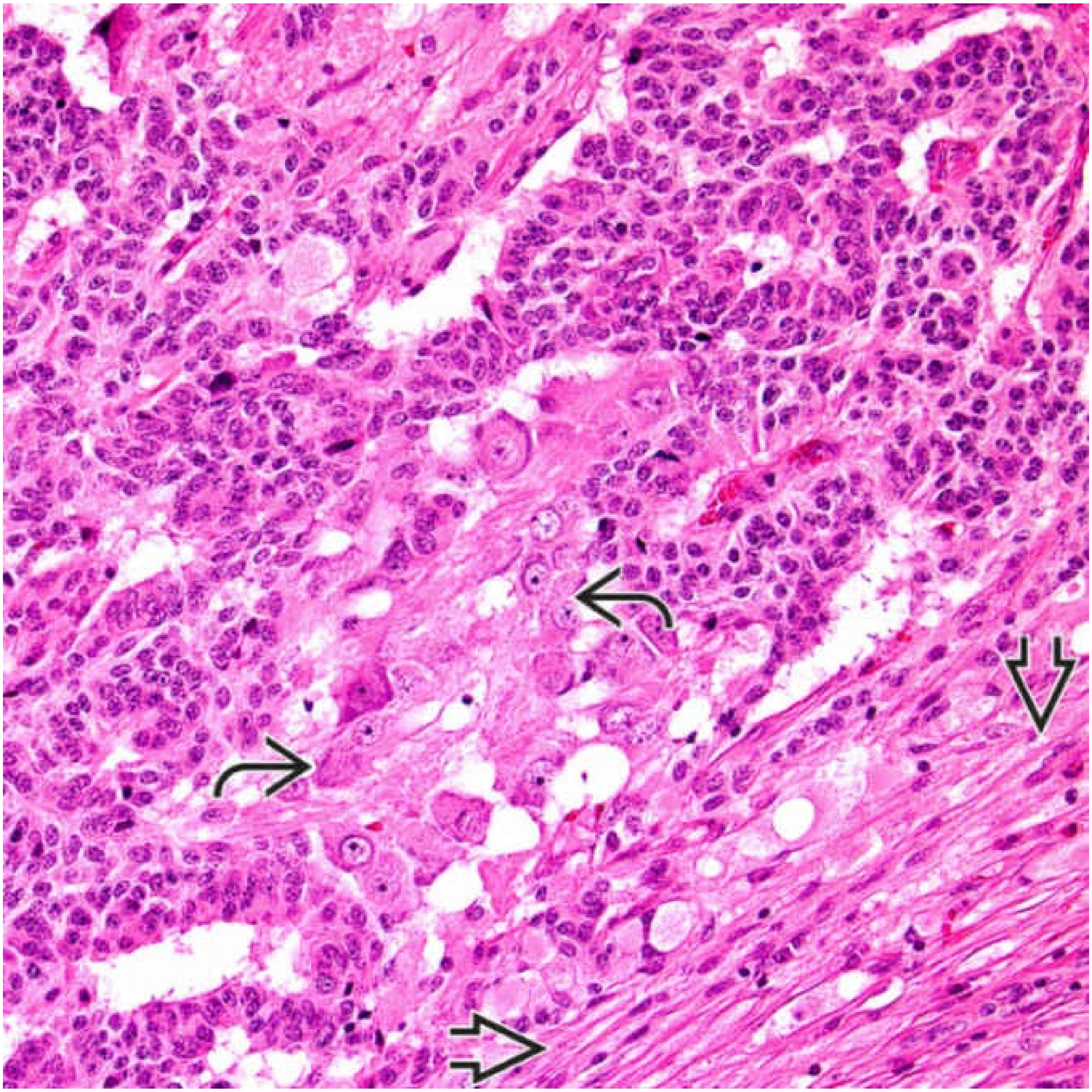
- Epithelioid, spindled, and ganglion-like cells present in varying proportions
- Endocrine cells may also be present
- S100 may reveal sustentacular-like cells surrounding nests of epithelioid cells
- No mitoses or necrosis

Diagnostic Checklist

• Low-grade neuroendocrine tumor
• Ampullary carcinoma
• Ganglioneuroma
• Neurofibroma
• Gastrointestinal stromal tumor

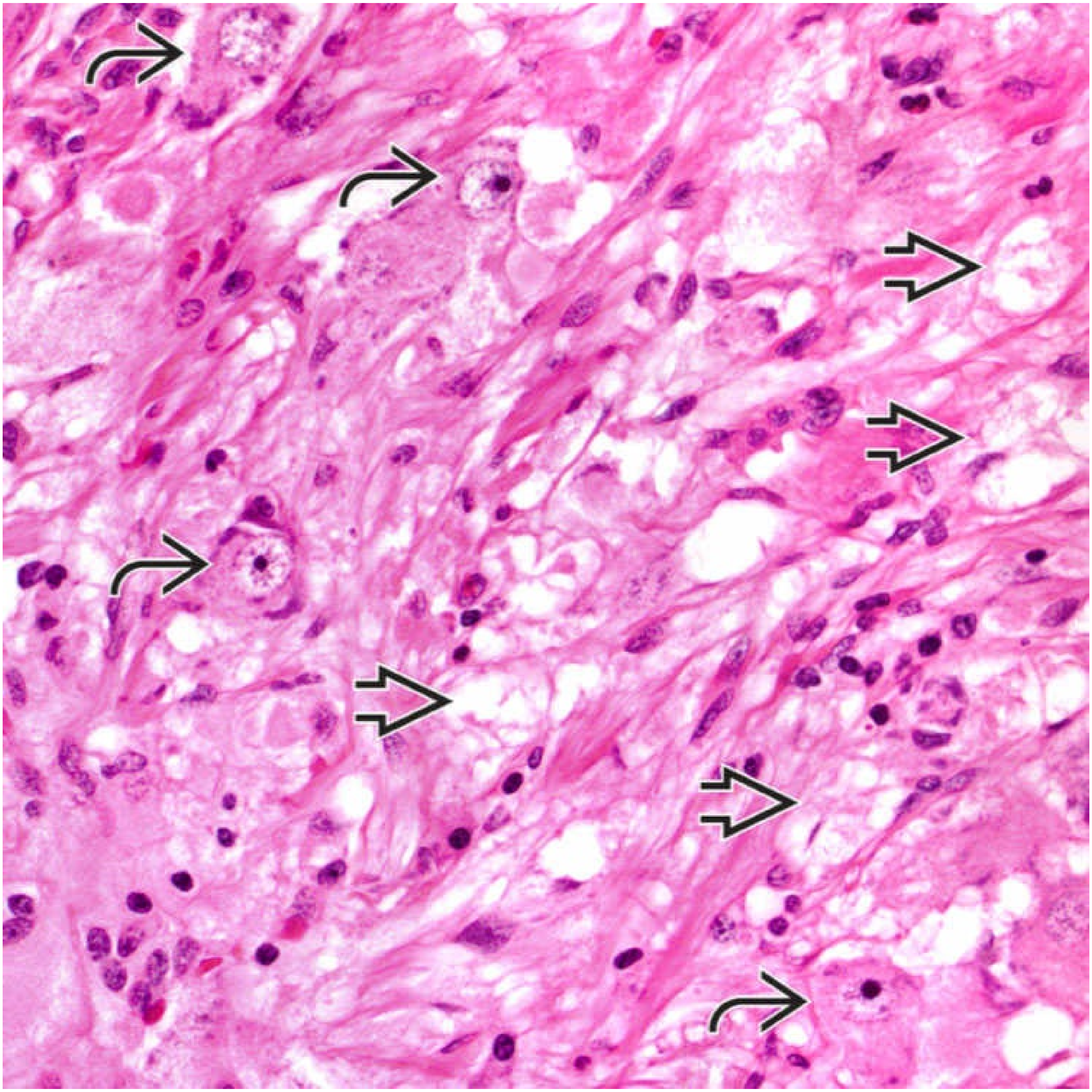


Periampullary Gangliocytic Paraganglioma
Periampullary gangliocytic paragangliomas ⇒ often have an infiltrating pattern at the periphery as shown here at low-power magnification. The lesion is centered in the submucosa with extension into the overlying mucosa ⇒ .



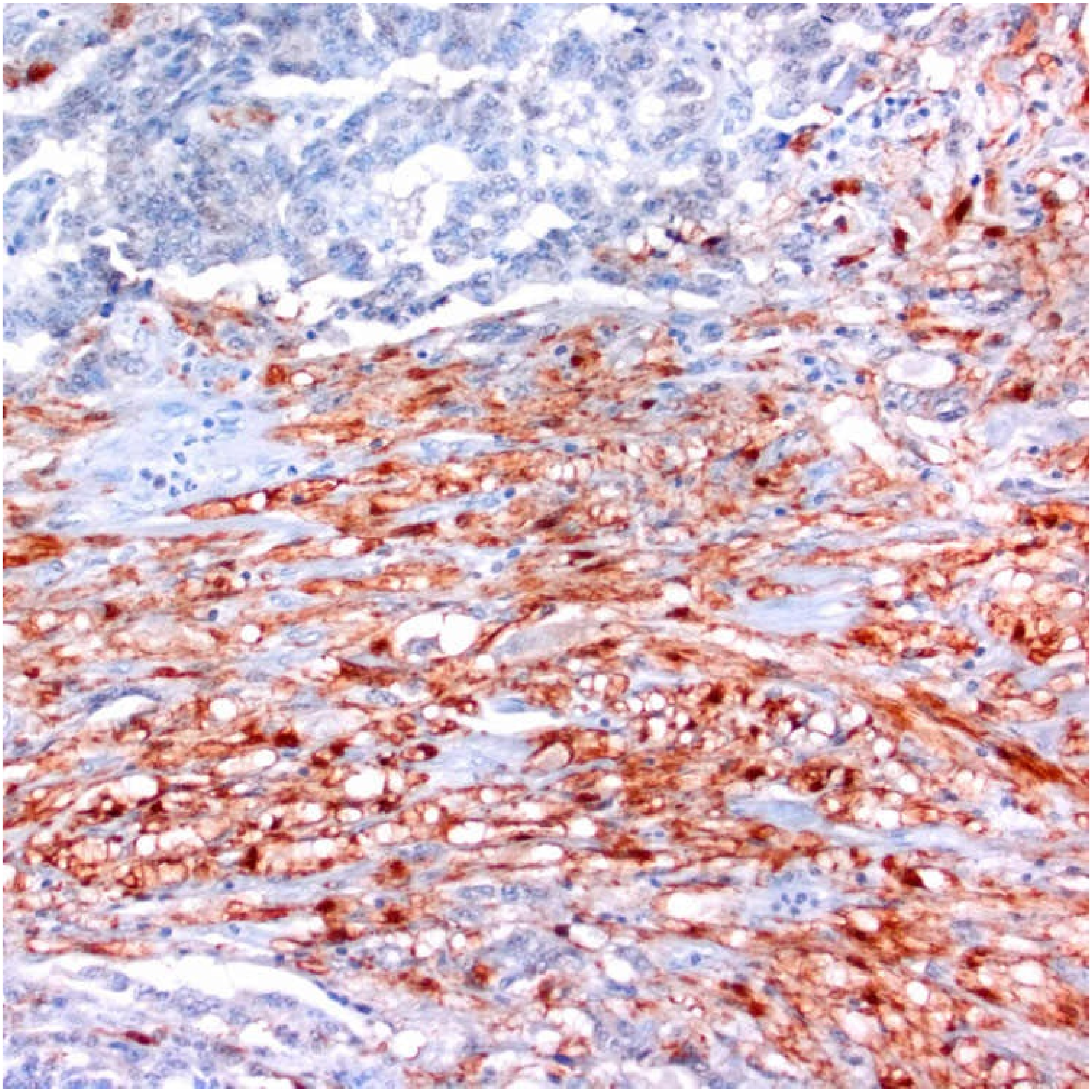
Gangliocytic Paraganglioma

Gangliocytic paraganglioma (high-power magnification) consisting of a mixture of epithelioid cells, ganglion-like cells ↷, and nerve sheath elements ⇨ is shown.



Gangliocytic Paraganglioma

Ganglion-like cells ↷ with dense cytoplasm, open chromatin, and prominent nucleoli are indistinguishable from normal ganglion cells. Nerve sheath elements ⇨ contain Schwann cells with elongated nuclei and vacuolated cytoplasm. Neural filaments are not well visualized.


Immunohsitochemistry for S100
As is typically seen, the Schwann cell component is positive for S100 in this gangliocytic paraganglioma.

TERMINOLOGY

Synonyms

- Gangliocytic paraganglioma
- Nonchromaffin paraganglioma

Definitions

- Neoplasm consisting of epithelioid, ganglion-like cells and nerve sheath elements

    - Associated with neurofibromatosis type 1 in some cases

ETIOLOGY/PATHOGENESIS

Origin

- Several theories
    - Progenitor neural crest cells
    - Embryonic celiac ganglion
    - Endodermally derived epithelial cells originating from ventral primordium of pancreas (hamartomatous proliferation)
    - Pancreatic tumor composed of ganglion-islet cell complexes

CLINICAL ISSUES

Epidemiology

- Incidence
    - Uncommon (1.2% of ampullary neoplasms in one series)
        - Associated with neurofibromatosis 1
- Age
    - 3rd-9th decades; mean: 6th decade
- Sex
    - Men slightly out number women (1.7:1.0)

Site

- Vast majority involve 2nd portion of duodenum (periampullary duodenum)
    - Extraduodenal sites include jejunum, pylorus, and lung

Presentation

- GI bleeding, abdominal pain, obstructive jaundice (less frequent)

Treatment

- Snare polypectomy or ampullectomy for smaller lesions
- Surgical resection (Whipple procedure) for larger lesions

Prognosis

- Vast majority benign
    - Few reports of regional lymph node metastases &/or recurrence
- No distant metastases or death associated with disease has been reported

MACROSCOPIC

General Features

- Sessile or pedunculated, centered in submucosa
- Ulceration of overlying mucosa is common
- Tan to white and moderately firm

Size

- 1-4 cm, although larger tumors are occasionally seen

MICROSCOPIC

Histologic Features

- 3 elements in varying proportions
  - **Epithelioid cells**
    - – Anastomosing cords and trabeculae
    - – Small, monotonous cells with round nuclei, stippled chromatin, eosinophilic cytoplasm, small nucleoli
    - – Positive for NSE, chromogranin, synaptophysin, somatostatin; variable marking with keratin, pancreatic polypeptide, somatostatin
  - **Ganglion-like cells**
    - – Abundant eosinophilic cytoplasm with large eccentric nuclei and prominent nucleoli
    - – Can look like normal ganglion cells or transitional epithelioid cells with less cytoplasm and inconspicuous nucleoli
    - – Positive for neurofilament markers, NSE; variably present endocrine-associated hormones
  - **Spindled cells**
    - – Indistinguishable from Schwann cells
    - – Elongated cells with tapered ends, faintly eosinophilic cytoplasm, elongated nuclei
    - – Positive for neurofilament markers, S100, NSE
  - Endocrine cells may also be present
  - S100 may reveal sustentacular-like cells surrounding nests of epithelioid cells
- Growth pattern is infiltrative with entrapment of smooth muscle or ductular structures
- No mitoses or necrosis

DIFFERENTIAL DIAGNOSIS

Low-Grade Neuroendocrine Tumor

- Positive for pancreatic polypeptide, keratins
- Lacks ganglion-like and spindled cells

Ampullary Carcinoma

- Strongly positive for keratins
- Nuclear atypia, mitoses, necrosis, and architectural complexity
- Lacks ganglion-like and spindled cells

Ganglioneuroma

- Lacks epithelioid component

Neurofibroma

- Lacks epithelioid and ganglion-like cells

Gastrointestinal Stromal Tumor

- C-kit or DOG1 positive

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- Periampullary tumors with any of 3 elements should be carefully examined for others

SELECTED REFERENCES

1. Sundararajan, V, et al. Duodenal gangliocytic paraganglioma with lymph node metastasis: a case report and review of the literature. *Arch Pathol Lab Med*. 2003; 127(3):e139–e141.
2. Sakhuja, P, et al. Periampullary gangliocytic paraganglioma. *J Clin Gastroenterol*. 2001; 33(2):154–156.

Specimen Handling, Whipple

Whipple (Pancreaticoduodenectomy) Procedure

Major Components

- Duodenum
  - May or may not include pylorus, depending on whether it was pylorus-sparing procedure
- Ampulla of Vater
- Common bile duct
- Pancreas

Anatomic Orientation

- Duodenum
  - Free proximal end usually shorter than free distal segment
  - Small portion of stomach usually attached to proximal end
  - Distal end may be either duodenum or jejunum
- Common bile duct
  - Sometimes green in color
  - Posterior and superior to pancreas
  - May be easier to identify from ampulla than from transected end
  - If gallbladder is present, can identify insertion of cystic duct and follow to common bile duct
- Ampulla of Vater
  - Usually obvious within duodenum, unless obscured by tumor
  - Some patients have accessory ampulla that drains accessory duct of Santorini
- Pancreas
  - General anatomic features
    - Retroperitoneal organ located in C-groove of 2nd part of duodenum
    - Anterior to pancreas is free space (omental bursa/lesser sac), and then posterior aspect of stomach
  - Anatomic divisions of pancreas
    - Head: To right of superior mesenteric vein/portal vein confluence; includes uncinate process
    - Neck: Constricted region to left of head
    - Body: Between superior mesenteric vein/portal vein confluence and aorta
    - Tail: Between aorta and splenic hilum
  - Pancreatic duct
    - Usually main pancreatic duct drains bulk of gland into duodenum at major duodenal papilla (ampulla) along with common bile duct
    - Normal diameter is < 1 cm

Specimen Handling

- Identify proximal end of duodenum
  - Usually shorter than distal end
- Head of pancreas sits in duodenal C-loop
  - Neck margin can be identified as oval-shaped transected pancreatic surface with central duct
- Determine anterior vs. posterior pancreatic surface
  - Anterior pancreatic surface bulges
  - Posterior pancreatic surface is flat
    - Common bile duct is superior to pancreas near 1st part of duodenum
- Adsay trapezoid method of orientation
  - Useful method to identify essential margins/surfaces
  - Place proximal intestinal margin to left, distal intestinal margin to right, and medial aspect of pancreas facing toward you
  - Visualize trapezoid
    - Left nonparallel side represents pancreatic neck margin
    - Right nonparallel side is uncinate margin
    - Space between sides is vascular groove
    - Anterior surface is base, and posterior surface is parallel opposite side
- Hand method of orientation
  - Curled left hand resembles pancreas enveloping superior mesenteric artery and portal vein
  - Thumb is uncinate process; flat fingers are neck, body, tail

Surgical Margins

- Common bile duct (shave margin)
  - Pancreatic resection (shave margin to include duct)
  - CAP calls this distal margin
  - AJCC calls this pancreatic neck margin
- Uncinate/retroperitoneal (perpendicular margin)
  - CAP: Uncinate
  - AJCC: Retroperitoneal
  - Should be inked, sectioned perpendicularly, and entire area submitted
  - Additional lymph nodes often found if this method is used
- Proximal and distal intestinal (or gastric)
  - Can be shave or perpendicular depending on distance from lesion
- Anterior surface is **not** surgical margin (because it is covered by smooth layer of peritoneum)
- Posterior surface: Controversial as to whether it is surgical margin
  - Consists of soft tissue between anterior surface of inferior vena cava and posterior aspect of pancreatic head and duodenum
  - During surgery, this is peeled off anterior surface of inferior vena cava
- Vascular groove or bed: Controversial as to whether it is surgical margin
  - Defined as indentation of superior mesenteric vein to portal vein confluence
  - Concave and smooth and glistening aspect of specimen between pancreatic neck and uncinate margins
- Note if tumor involves any margins grossly

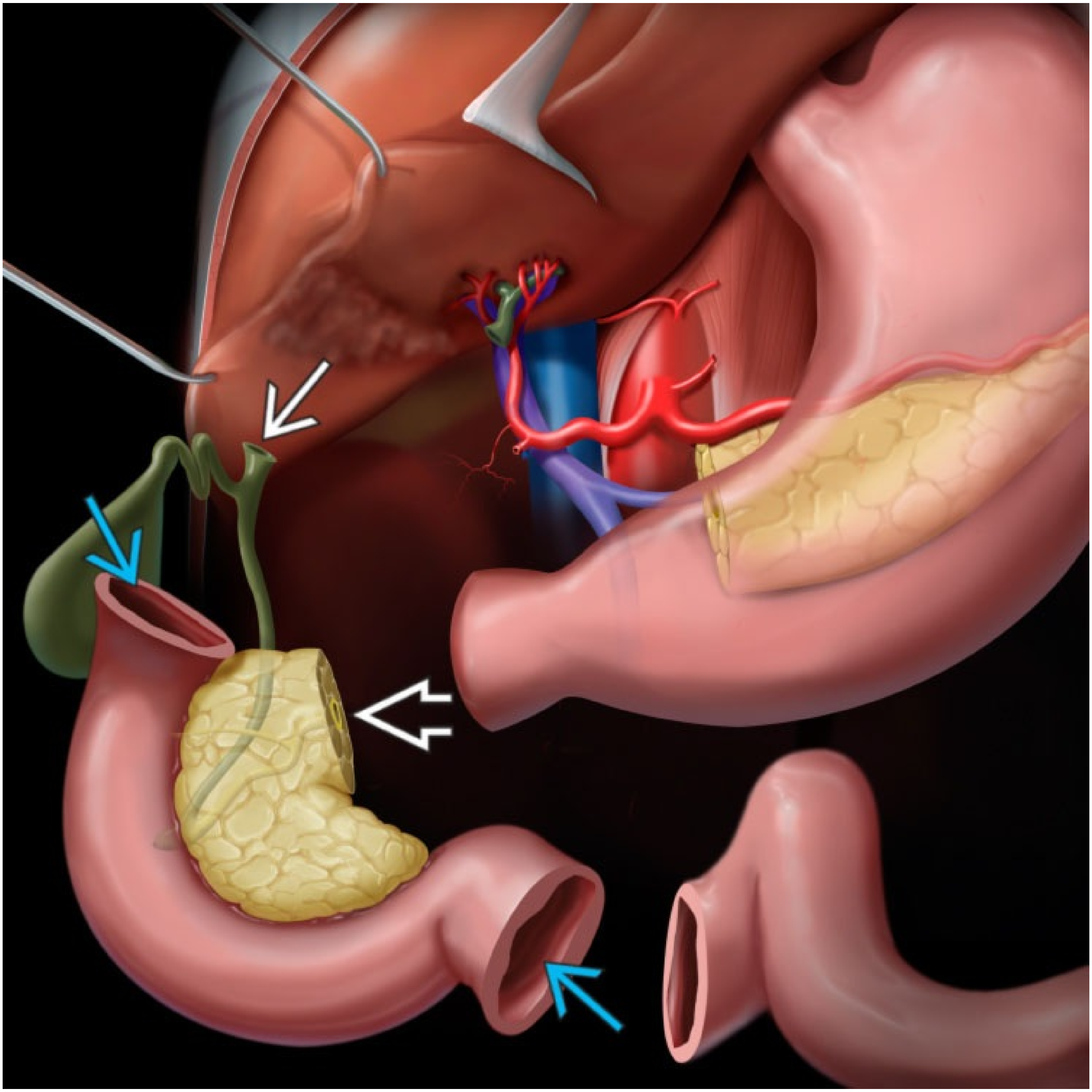
Dissection

- Measure dimensions of important structures
  - Ink surface of pancreas and uncinate/retroperitoneal margin area
  - Take margins, as above
  - Open duodenum along side opposite pancreas
  - ○ Document any lesions
  - ○ If tumor involves ampulla, determine epicenter of tumor
  - – Is papilla or adjacent duodenal mucosa involved by tumor?
  - – Does tumor expand ampulla or form thick rind-like mass along duct?
- ○ Note presence of tenacious mucin extruding through papilla (diagnostic of intraductal papillary mucinous tumor)
- Open common bile duct with small scissors
  - ○ May be easier to start at proximal end since duct is often dilated
  - ○ Extend incision down through ampulla of Vater
  - ○ Note any strictures or masses in bile duct or ampulla
  - ○ Ink common bile duct with color to distinguish it from pancreatic duct on microscopic sections
  - ○ Alternative method: Cannulate common bile duct and pancreatic duct with probes, then make single cut that bivalves pancreas and ducts
- Examine pancreas
  - ○ "Bread-loaf" pancreas into thin slides perpendicular to long axis of duodenum
    - – Leave each slide thinly attached to duodenum for orientation
  - ○ Ascertain if ducts are dilated, stenotic, or thickened
  - ○ Note if there is cystic tumor communicating with pancreatic duct (main or branch ducts)
  - ○ Note luminal contents of ducts
  - ○ Note if tumor extends into peripancreatic soft tissue grossly
- Find lymph nodes
- Main questions to answer during dissection
  - ○ Is there a tumor?
  - ○ Where is tumor?
    - – What is site of origin, and what structures are involved?
  - ○ How big is tumor?
  - ○ What is appearance of tumor (solid, cystic, etc.)?
    - – If tumor is cystic, document cyst contents: If multi-/unilocular, size of cysts, and presence of mural nodules
    - – If cystic tumor is mucinous, entire tumor should be submitted
  - ○ How many lymph nodes are there, and what is their gross appearance?

Histologic Sections

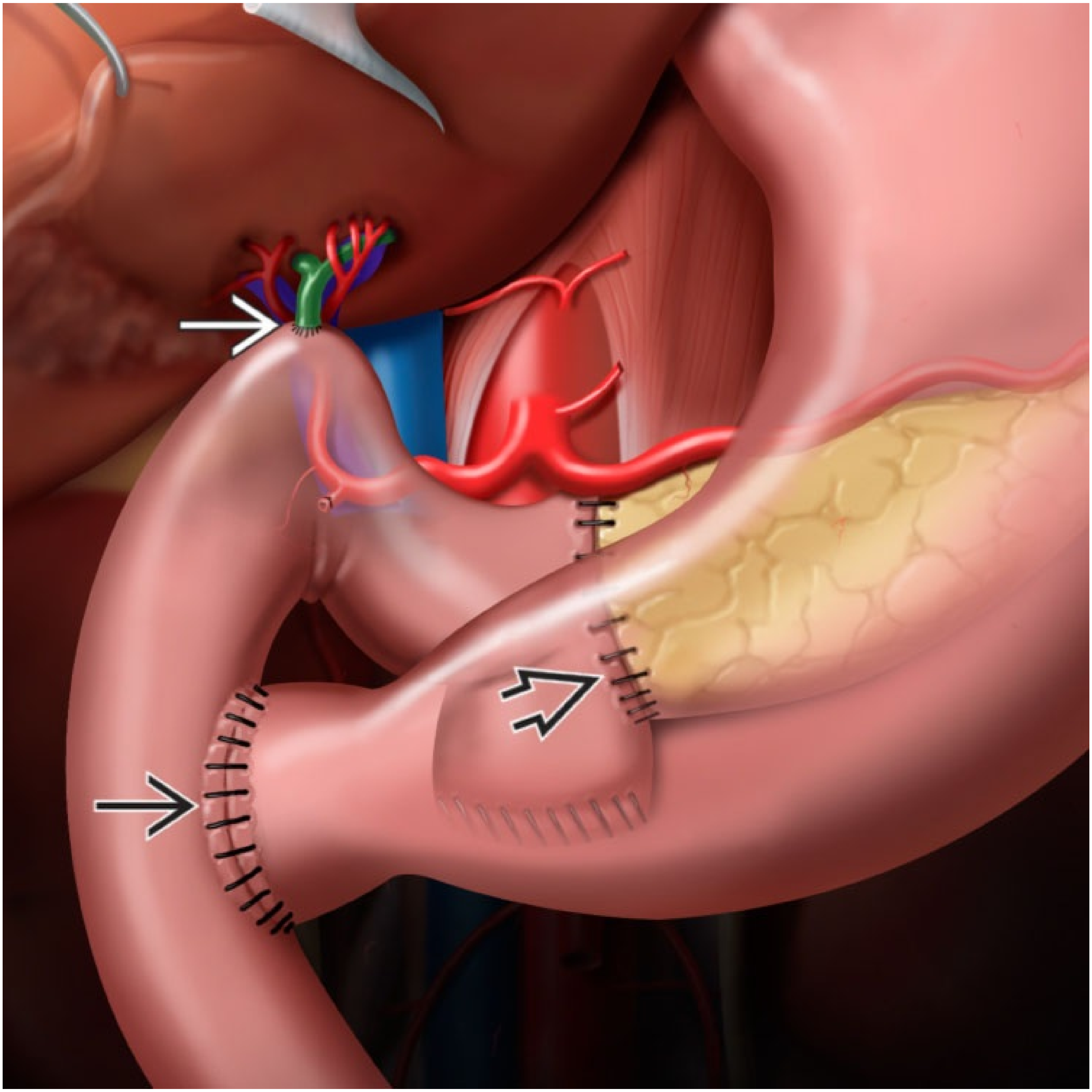
- Margins, as detailed above
  - Tumor
  - ○ Demonstrate relationship to ampulla, pancreas, pancreatic duct, common bile duct, and duodenum
  - – Sections parallel to long axis of bile duct (including duodenum, ampulla, bile duct, and pancreas all in 1 section) can be very helpful

- Posterior surface of pancreas
  - Palpate (if tumor appears close), ink, and take perpendicular sections
- Anterior surface of pancreas
- Sections of interface between tumor and normal
- Sections of normal uninvolved parenchyma
  - At least 1 section from anterior and posterior halves
- Sections of ampulla and accessory ampulla if present



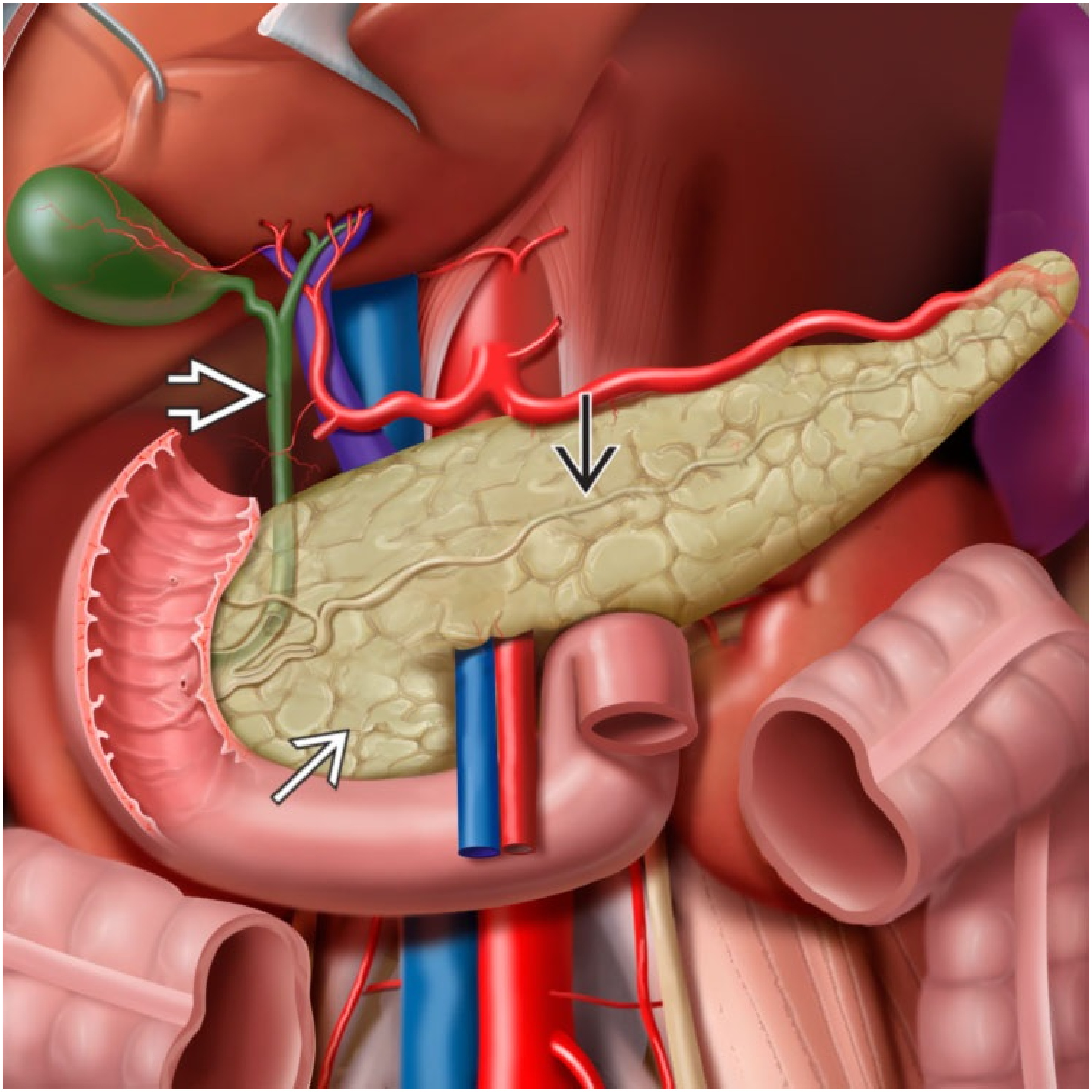
Whipple Procedure

Graphic shows the Whipple (pancreaticoduodenectomy) procedure. Note the common bile duct margin ⇒, the pancreatic margin ⇒, and the intestinal margins →.



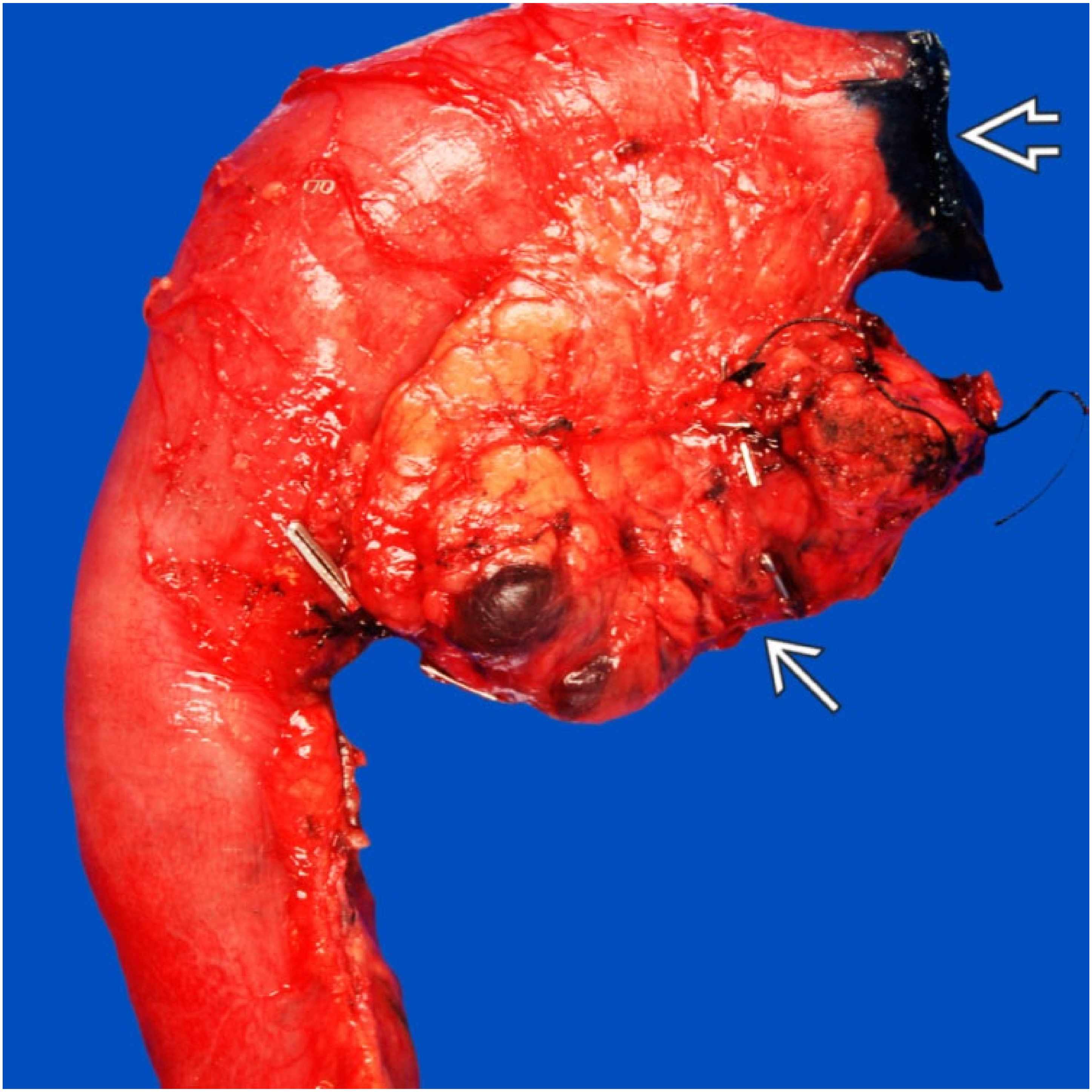
Reanastomoses

Graphic depicts the reanastomoses after a Whipple procedure, including the anastomoses between the small bowel and the stomach →, the pancreas ⇨, and the bile duct ⇒ .



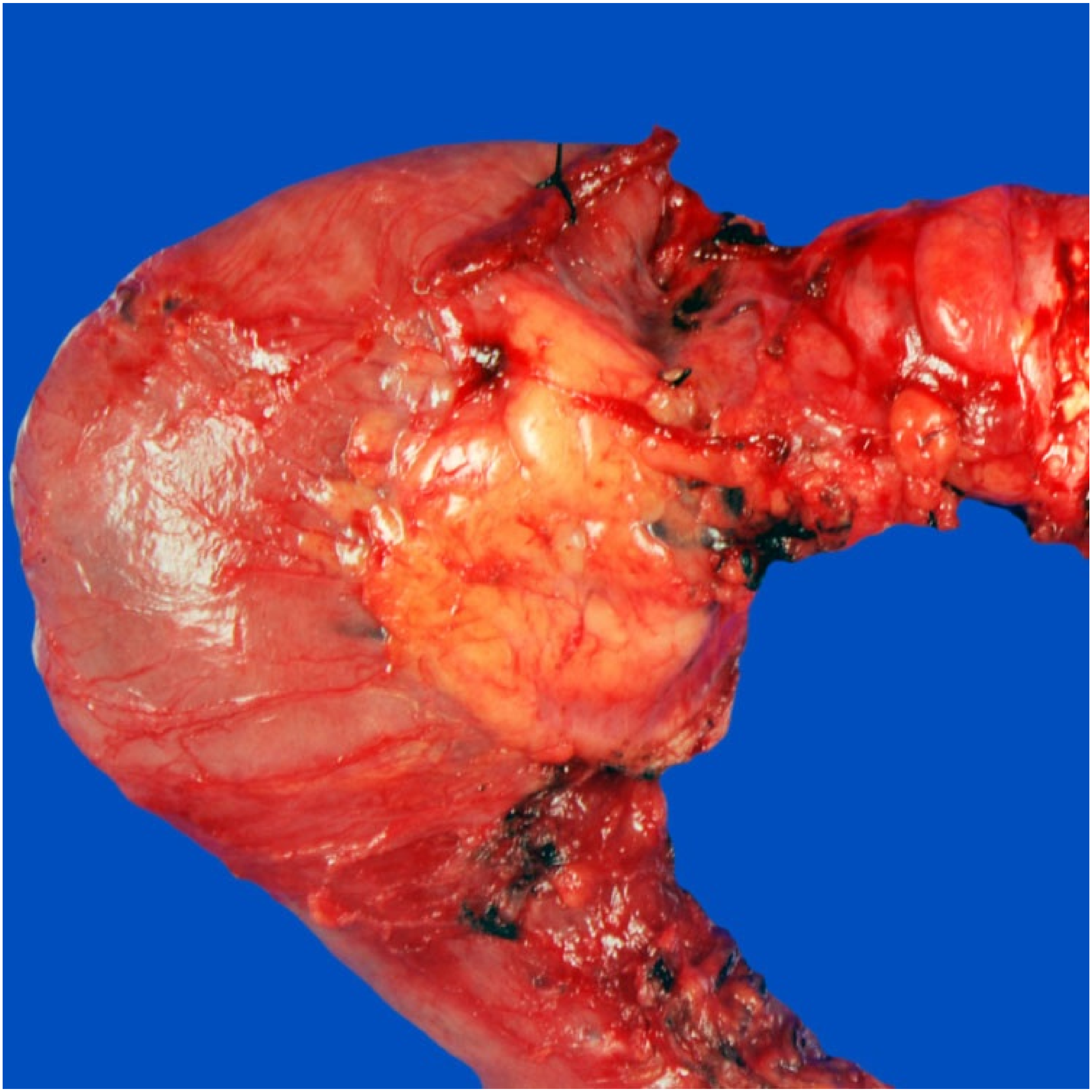
Anatomy

The pancreas lies within the C-loop of the duodenum. The head of the pancreas is nearest to the duodenum ⇒. The main pancreatic duct → and the common bile duct ⇨ converge at the ampulla.

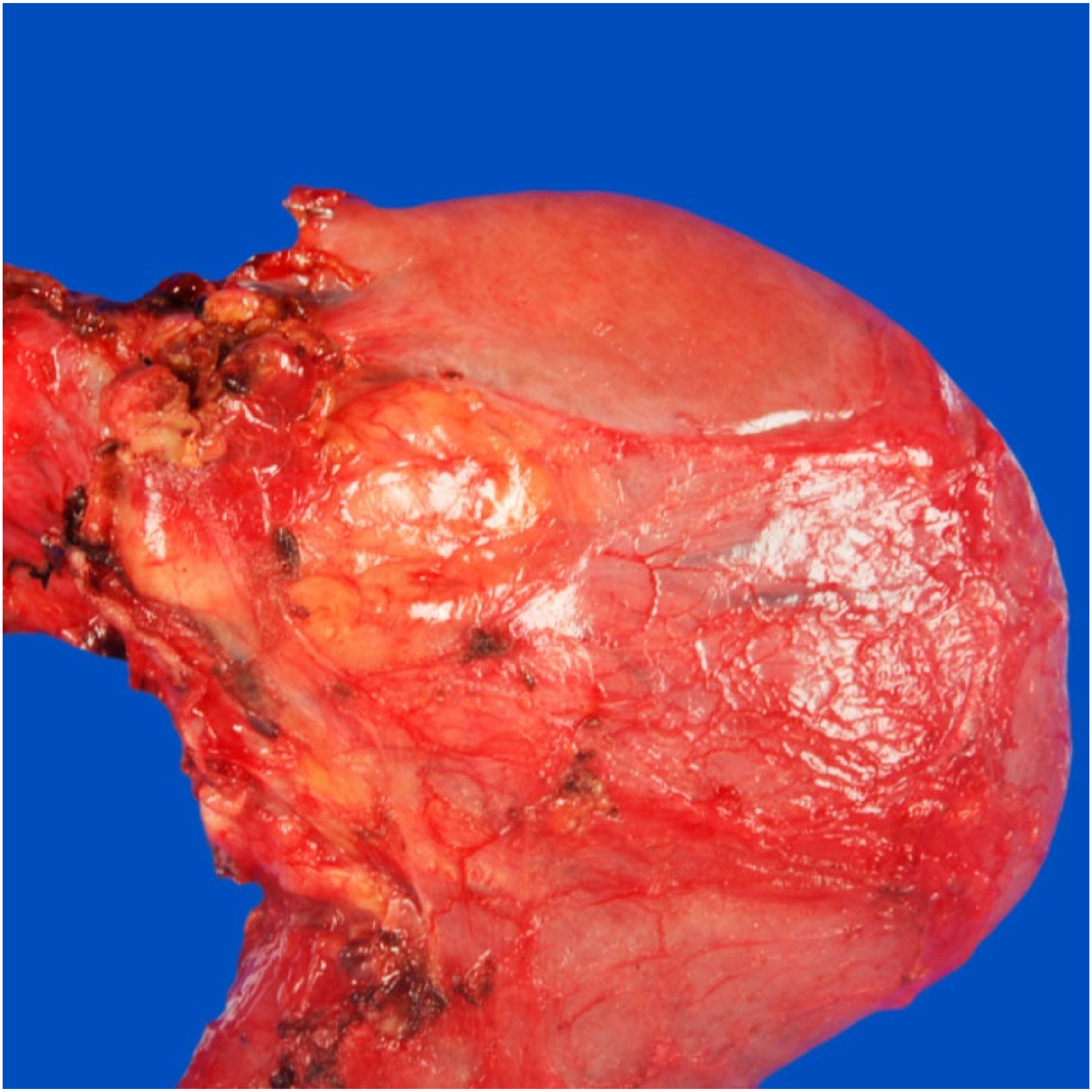


Pancreas and Duodenum

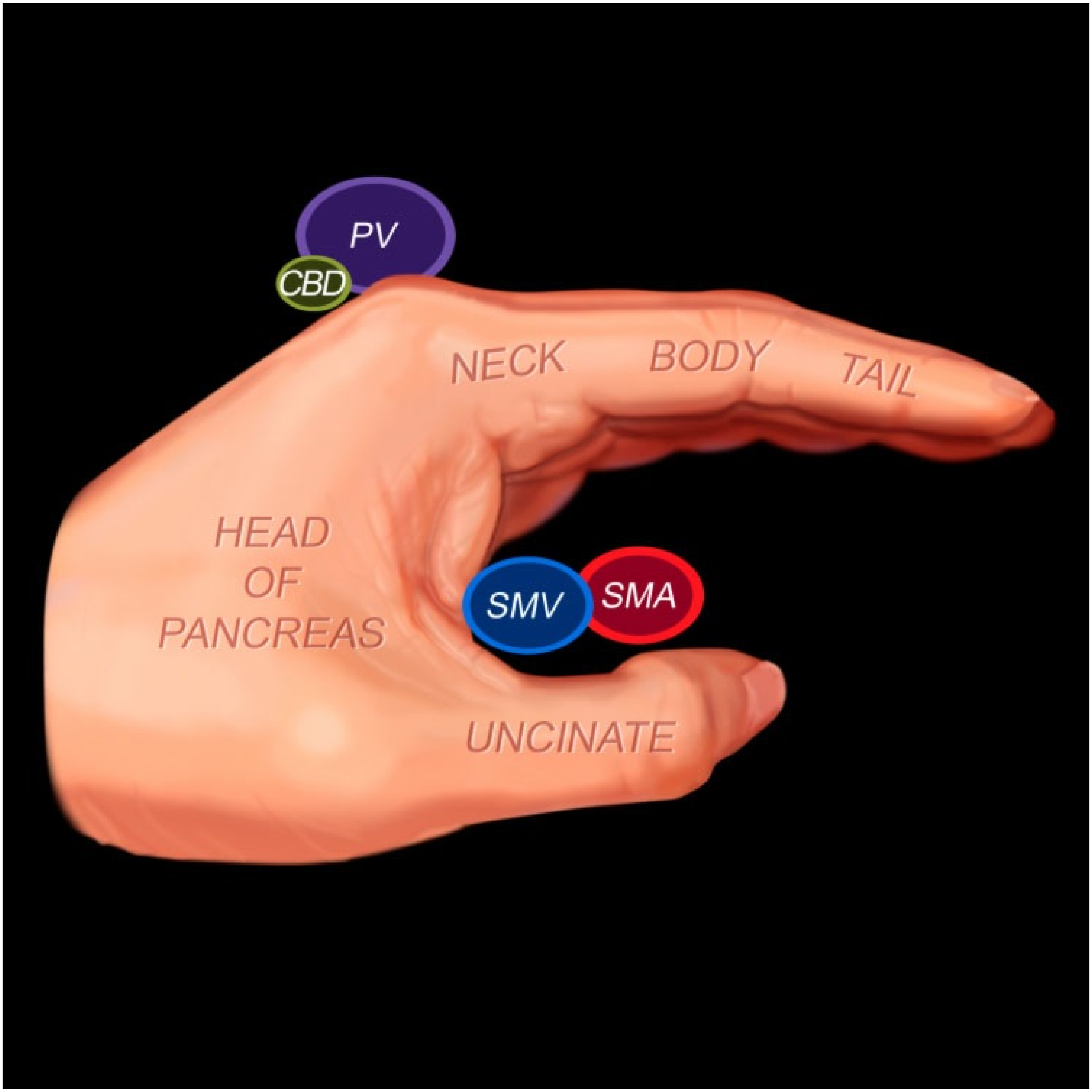
The pancreas ⇨ lies within the C-loop of the duodenum. The shorter segment of bowel is the proximal end ⇨, and the longer segment of bowel is the distal end.



Anteromedial Pancreas
The anteromedial surface of the pancreas bulges and is fatty.

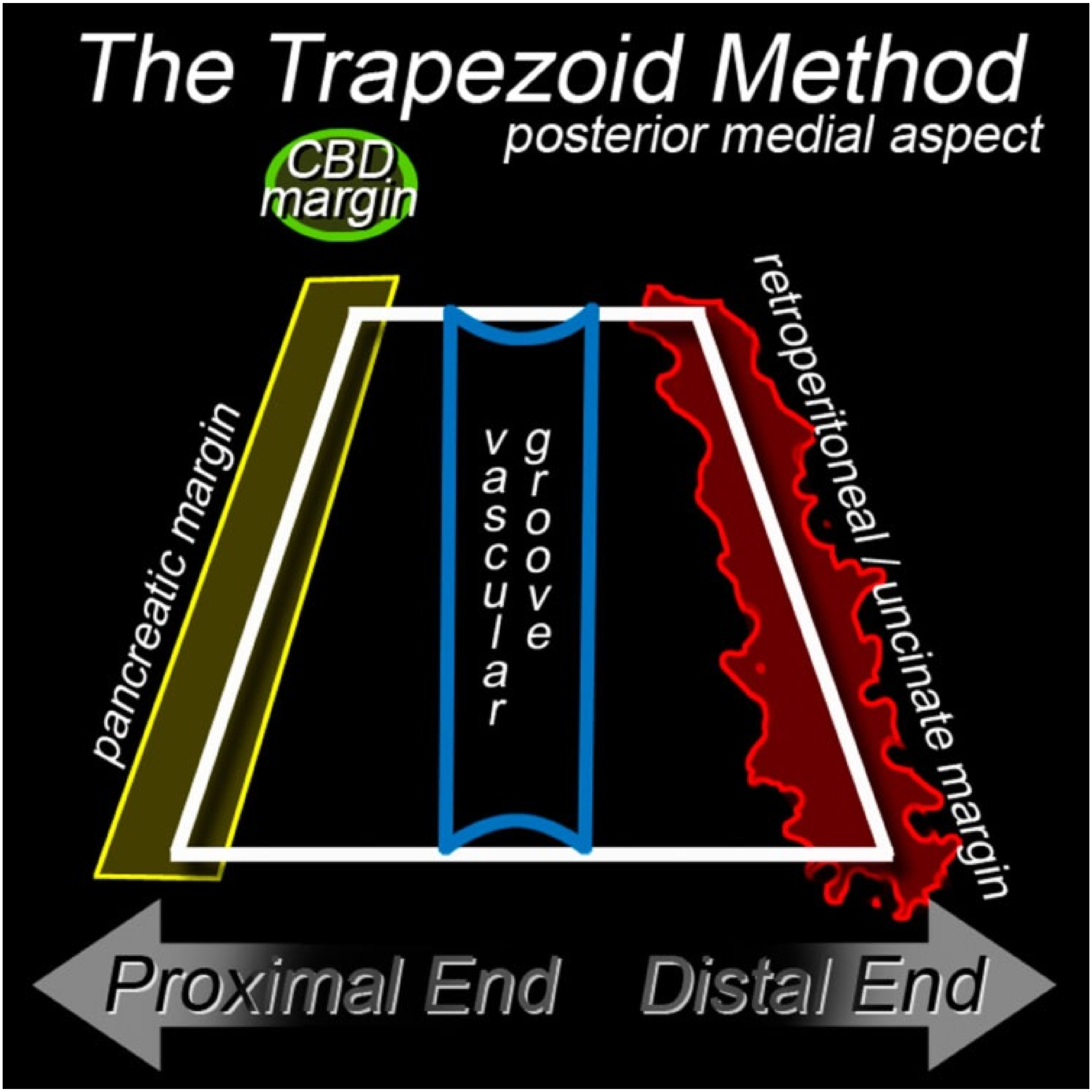


Posterior Surface of Pancreas
The posterior surface of the pancreas is flat.

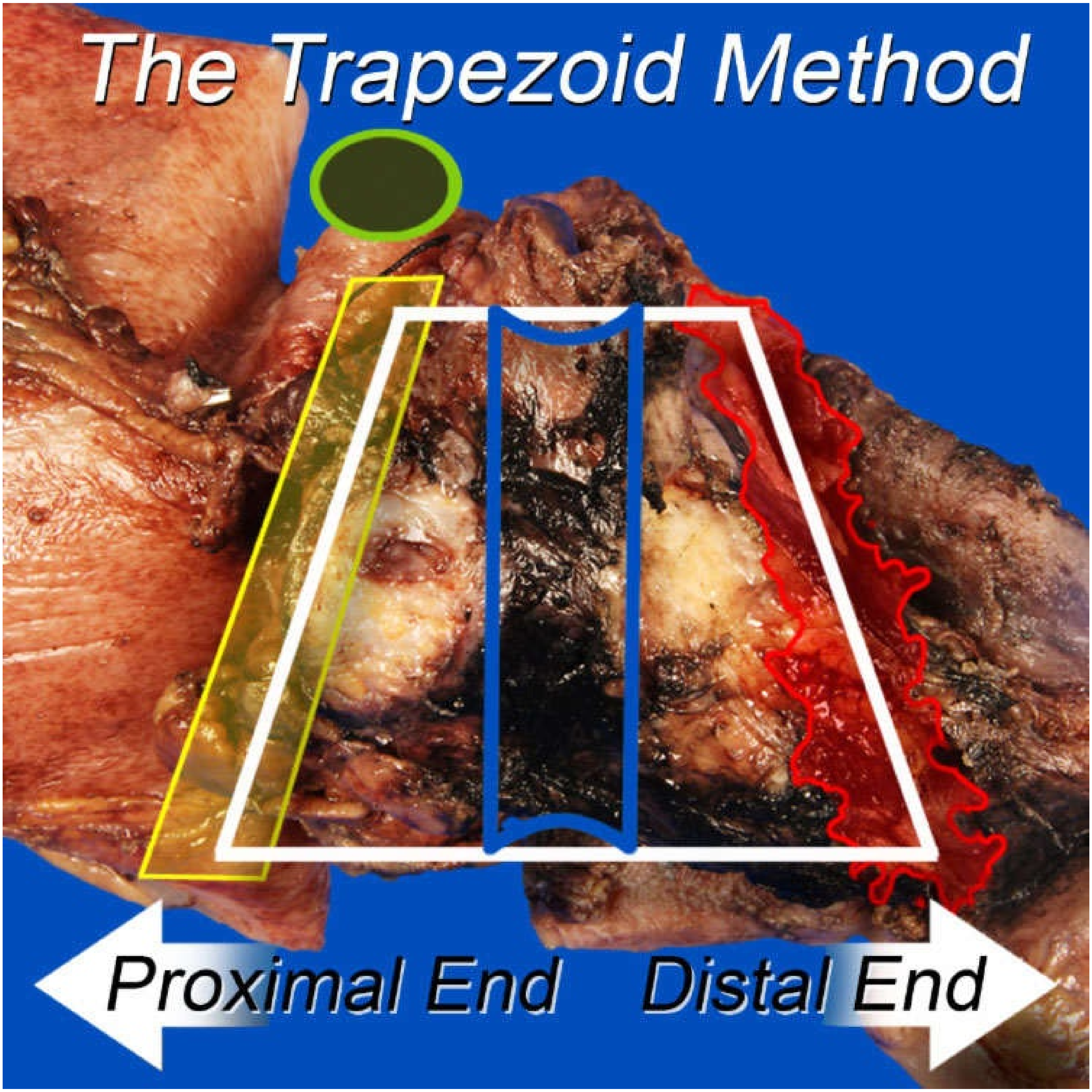


Hand Method of Whipple Specimen Orientation

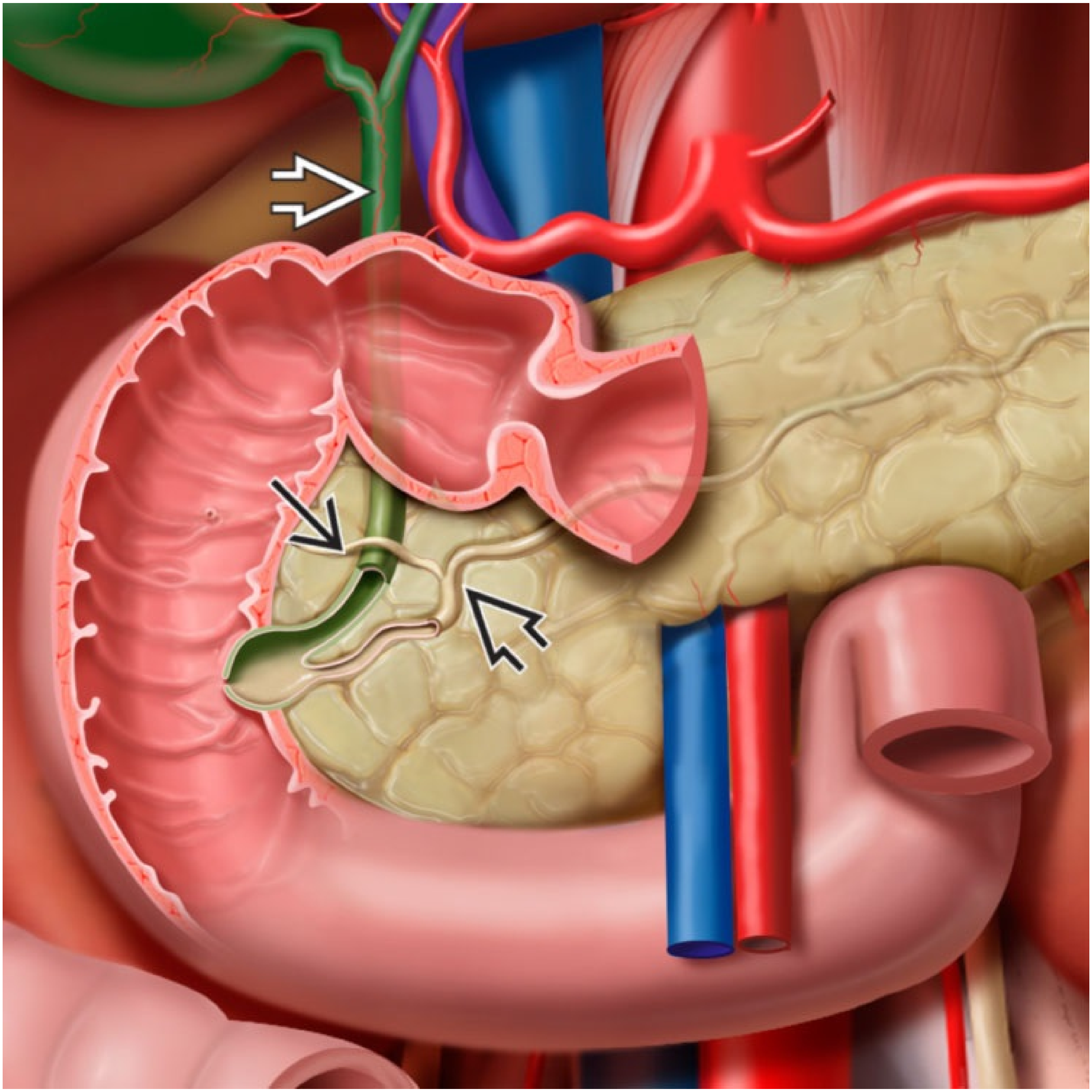
You can use your left hand to help orient the anterior view of the pancreas. The hooked thumb is the uncinate process, and the superior mesenteric vein and superior mesenteric artery rest in the vascular groove. The flattened fingers represent the neck, body, and tail of the pancreas.



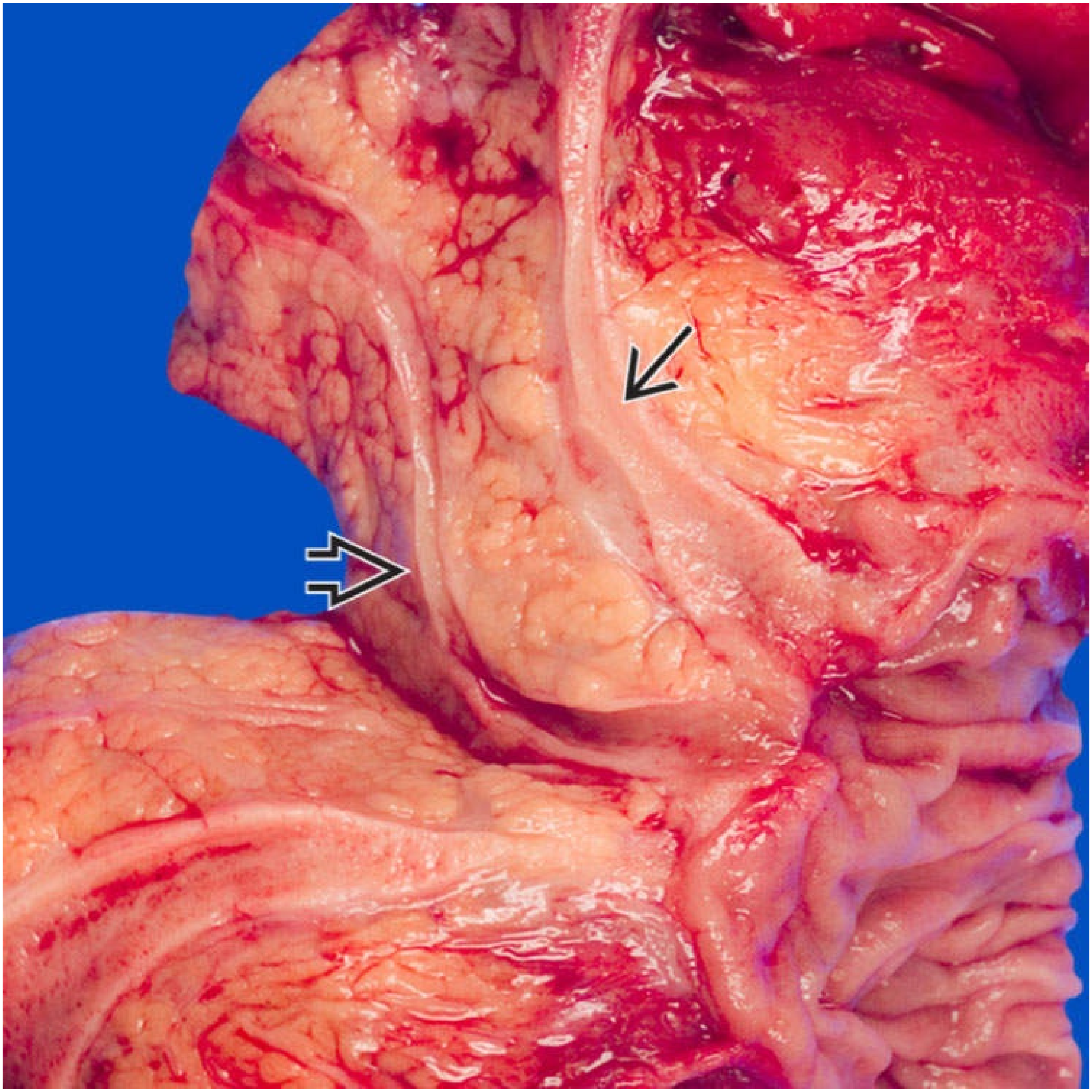
Adsay Trapezoid Method of Whipple Orientation
Graphic illustrates the Adsay trapezoid method of orienting a Whipple specimen.



Trapezoid Method and Gross Specimen
Superimposing the trapezoid graphic on a gross specimen, the vascular groove is within the blue lines, the retroperitoneal margin is within the red lines, and the pancreatic margin is within the yellow lines.

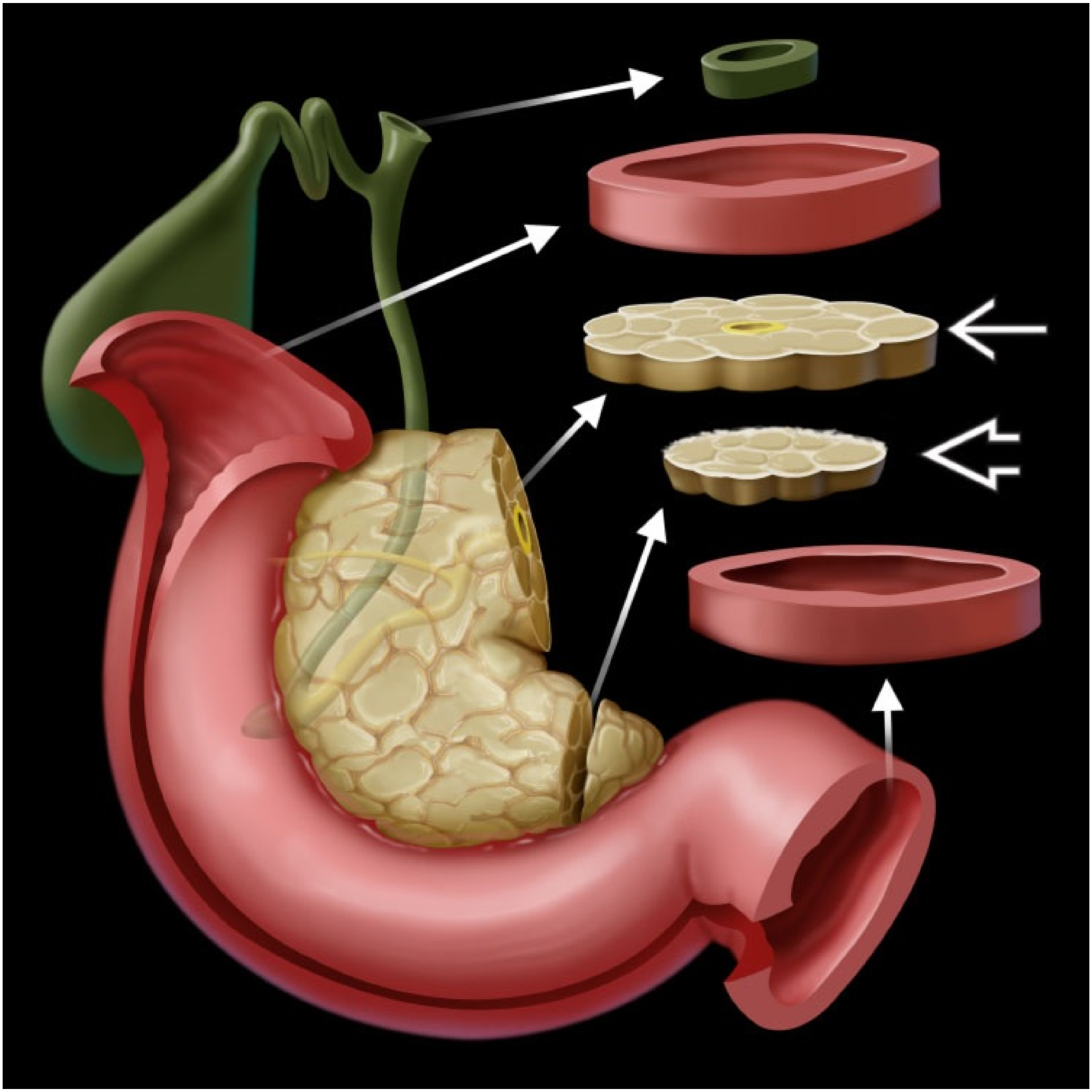


Anatomy of Common Bile Duct and Pancreatic Duct
Graphic illustrates the anatomy of the common bile duct ⇨ and the pancreatic duct. The pancreatic duct makes a right-angle turn ⇨ with the head of the pancreas. Note the accessory pancreatic duct → that enters the duodenum at the minor papilla.



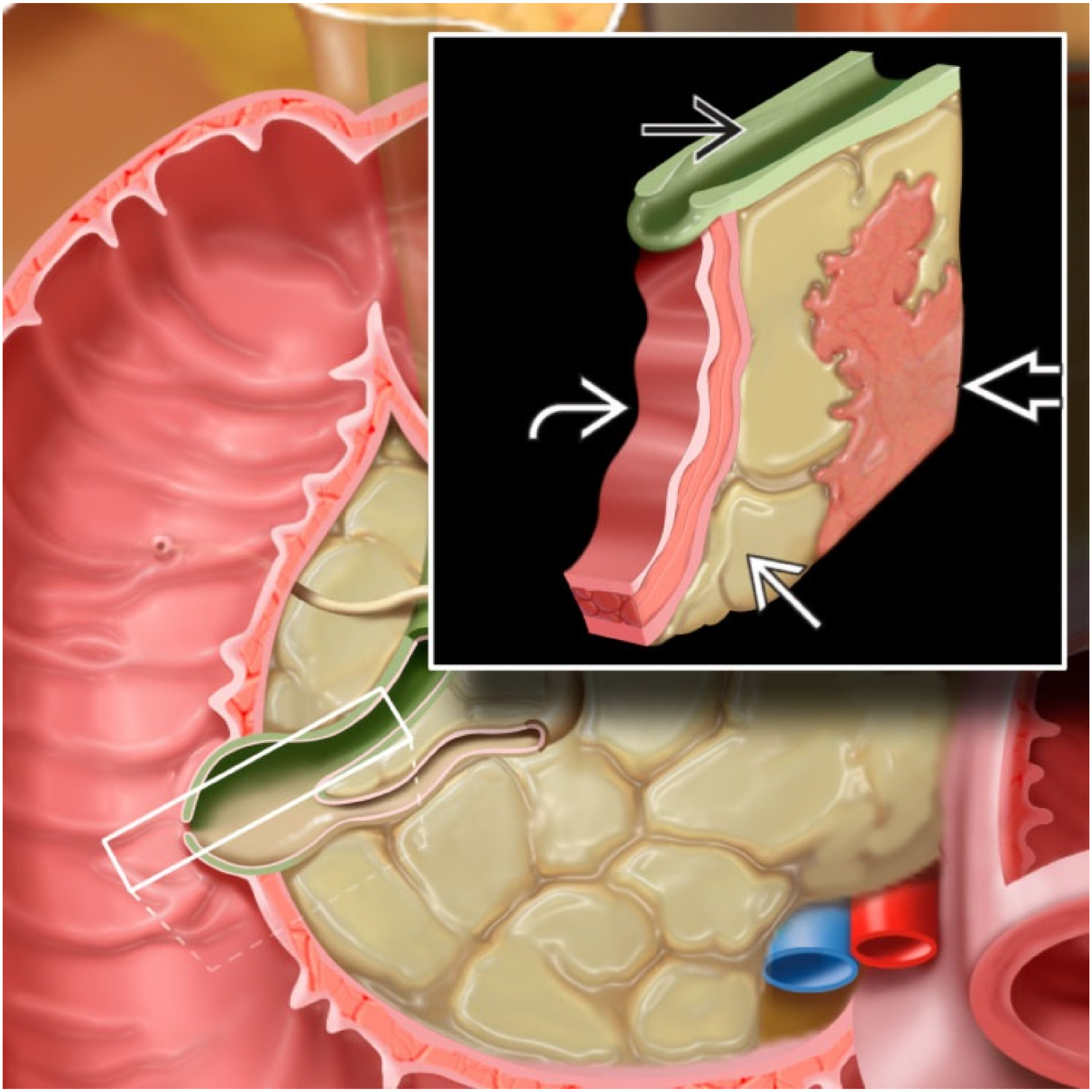
Common Bile Duct and Pancreatic Duct

This photo of a bivalved pancreas illustrates the pancreatic duct ⇨ and the common bile duct → entering the duodenum together at the ampulla. The pancreatic duct makes a right-angle turn with the head of the pancreas.

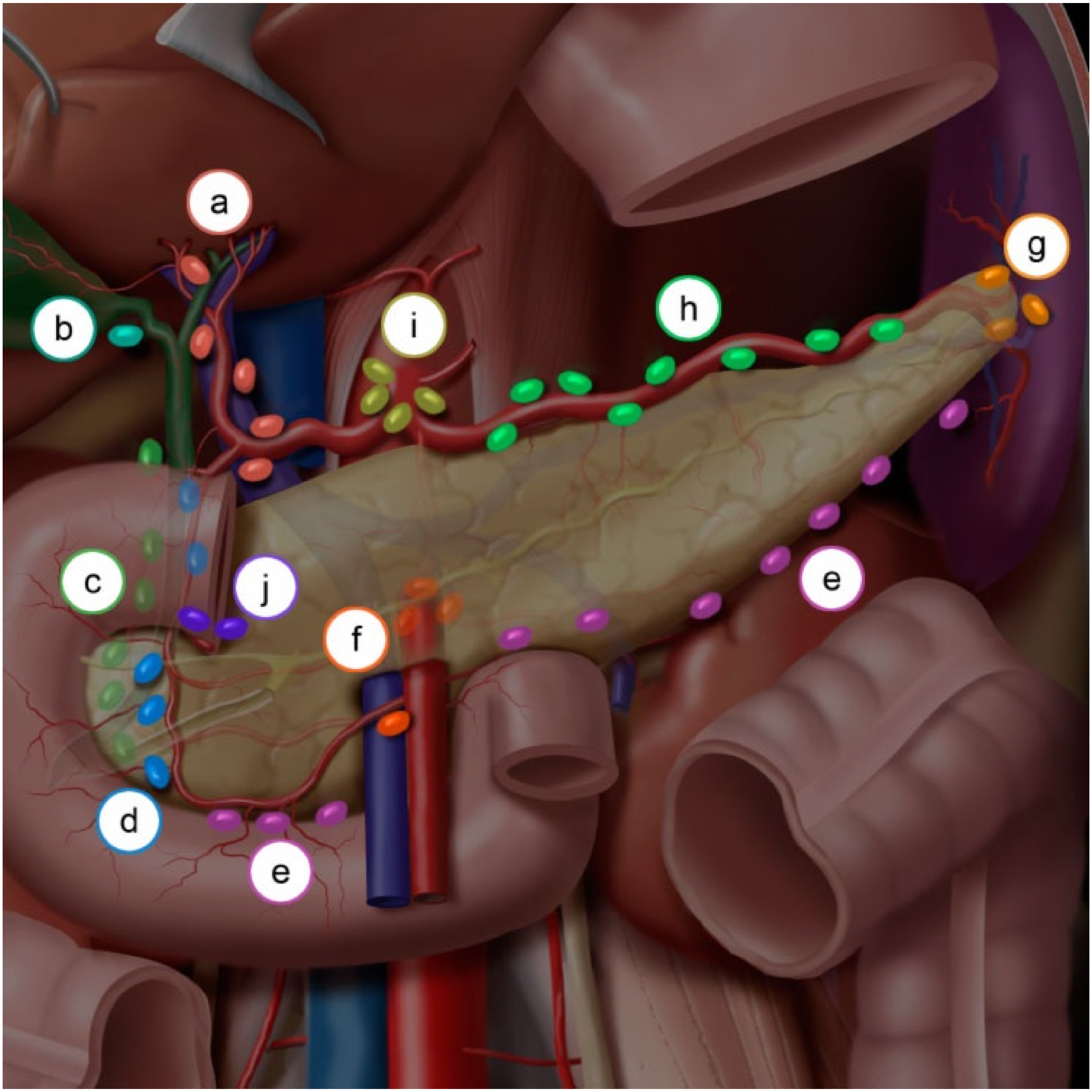


Whipple Margins

The important margins include the common bile duct, proximal and distal intestinal, pancreatic neck ⇒, and uncinate ⇨. The uncinate (retroperitoneal) margin should be inked, sectioned perpendicularly, and entirely submitted.



Tumor Section
A single section demonstrating the tumor in relationship to pancreas, common bile duct, and duodenum is often helpful.



Lymph Nodes

Graphic depicts the important peripancreatic lymph node groups: (a) Hepatic, (b) cystic duct, (c) posterior pancreaticoduodenal, (d) anterior pancreaticoduodenal, (e) inferior, (f) superior mesenteric, (g) splenic hilar, (h) superior, (i) celiac, and (j) pyloric. A minimum of 12 nodes is required for adequate staging.

SELECTED REFERENCES

1. Adsay, NV, et al. The number of lymph nodes identified in a simple pancreatoduodenectomy specimen: comparison of conventional vs orange-peeling approach in pathologic assessment. *Mod Pathol*. 2009; 22(1):107–112.
2. Riediger, H, et al. The lymph node ratio is the strongest prognostic factor after resection of pancreatic cancer. *J Gastrointest Surg*. 2009; 13(7):1337–1344.
3. Freelove, R, et al. Pancreatic cancer: diagnosis and management. *Am Fam Physician*. 2006;

73(3):485–492.
4. Westra, WH, et al. Surgical Pathology Dissection: An Illustrated Guide, 2nd ed. New York: Springer, 2002.
5. Strasberg, SM, et al. Evolution and current status of the Whipple procedure: an update for gastroenterologists. *Gastroenterology*. 1997; 113(3):983–994.

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